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Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Eplerenone

Proprietary Product Name: Inspra

Sponsor: Pfizer Australia Pty Ltd

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Second round report: 16 November 2012

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
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Contents

List of abbreviations	5
1. Clinical rationale	7
2. Contents of the clinical dossier	7
2.1. Scope of the clinical dossier	7
2.2. Paediatric data	7
2.3. Good clinical practice	8
3. Pharmacokinetics	8
4. Pharmacodynamics	8
5. Dosage selection for the pivotal studies	8
6. Clinical efficacy	8
6.1. Proposed additional indication	8
6.2. Evaluator's conclusions on clinical efficacy for the proposed additional indication	24
7. Clinical safety	25
7.1. Studies providing evaluable safety data	25
7.2. Patient exposure	26
7.3. Adverse events	27
7.4. Laboratory tests	30
7.5. Vital signs	32
7.6. Postmarketing experience	33
7.7. Other safety issues	33
7.8. Evaluator's overall conclusions on clinical safety	37
8. First round benefit-risk assessment	39
8.1. First round assessment of benefits	39
8.2. First round assessment of risks	40
8.3. First round recommendation regarding authorisation	41
9. Clinical questions	41
9.1. Efficacy	41
9.2. Safety	42
10. Second round evaluation of clinical data submitted in response to questions	43
11. Second round benefit-risk assessment	50
11.1. Second round assessment of benefits	50
11.2. Second round assessment of risks	50

11.3. Second round assessment of benefit-risk balance _____	50
12. Second round recommendation regarding authorisation ____	50
13. References _____	50

List of abbreviations

Abbreviation	Meaning
ACE-I	angiotensin converting enzyme inhibitors
ARB	Angiotensin II receptor blocker
bpm	Beats per minute
CHF	Chronic Heart Failure
CI	Confidence interval
CMI	Consumer Medicines Information
CRT	resynchronization therapy
CSR	Clinical Study Report
CV	Cardiovascular
DBP	Diastolic blood pressure
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration rate
EMA	European Medicines Agency
ESC	Executive Steering Committee
EU	European Union
e.g.	Exempli gratia; for example
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HF	Heart failure
HR	Heart rate
ICD	implantation of cardiac defibrillator
i.e.	Id est; that is
L	Litre
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
Mg	Milligram
mL	Millilitre
msec	milliseconds
NYHA	New York Heart Association

PI	Product Information
SAE	Serious adverse event
SD	Standard Deviation
SBP	Systolic blood pressure
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
U	Units
US	United States of America
≥	At or greater than
≤	At or lesser than
>	Greater than
<	Less than
vs.	Versus

1. Clinical rationale

Eplerenone is a selective mineralocorticoid receptor antagonist. Aldosterone, the receptor's predominant endogenous ligand, is involved in the pathophysiology of heart failure (HF) via its effects causing sodium retention, magnesium and potassium loss, sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, and impaired arterial compliance.

The sponsor made a reference to the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trial, which showed that mortality at 1 year was reduced by 31% in subjects with severe systolic HF (New York Heart Association [NYHA] class IV) treated with the angiotensin converting enzyme inhibitor (ACE-I), enalapril, compared to subjects treated with placebo. In this trial, subjects with high baseline plasma aldosterone levels had a higher mortality than subjects with lower baseline aldosterone levels. In addition, in the enalapril-treated group, mortality was reduced only in subjects with baseline aldosterone plasma levels above the median.

The sponsor also made a reference to the RALES study (Randomised Aldactone Evaluation Study), where the addition of the non-selective aldosterone blocker, spironolactone (25 mg daily), to standard therapy (ACE-I and loop diuretic) resulted in a 30% reduction in the relative risk of all-cause mortality in subjects with NYHA class III or IV HF.

In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), the registration Phase III study for eplerenone, results showed that eplerenone reduced mortality from any cause, as well as cardiovascular mortality or hospitalisation for cardiovascular events. Based on these results, eplerenone was approved in Australia to reduce the risk of cardiovascular death in patients who had evidence of HF and left ventricular impairment within 3-14 days of an acute myocardial infarction (AMI).

The sponsor stated that although HF is a progressive disease and the majority of patients with HF are either asymptomatic (NYHA class I) or have mild symptoms (NYHA class II), aldosterone antagonists have not been studied in NYHA class II HF patient population in randomised placebo-controlled trials. The clinical rationale for the study presented in this submission (Study A6141079) is to allow evaluation of the efficacy and safety of aldosterone blockade in the NYHA class II HF population.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The clinical dossier contains the clinical study reports of a pivotal study relating to the proposed extension of indications.

The submission contained the following clinical information

- 1 pivotal efficacy/safety study with 3 sets of CSRs: amended primary CSR, supplementary CSR and Open-Label Extension phase report. The reason for and the contents of the 3 sets of CSRs will be described below.

2.2. Paediatric data

The submission did not include paediatric data. The sponsor has also stated that there is no paediatric development program for eplerenone due to the low estimated incidence and prevalence of the current and proposed indication for eplerenone in the paediatric population.

2.3. Good clinical practice

The clinical study reviewed in this evaluation was in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.

3. Pharmacokinetics

No new data submitted.

4. Pharmacodynamics

No new data submitted.

5. Dosage selection for the pivotal studies

No new data submitted.

6. Clinical efficacy

6.1. Proposed additional indication

Of reducing the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II heart failure and left ventricular systolic dysfunction in addition to standard optimal therapy

A single clinical trial, Study A6141079 (study acronym: EMPHASIS-HF), was submitted in this application, but involved 3 sets of CSRs: the amended Primary CSR (amended pCSR), the Supplemental CSR (sCSR), and the Open-label extension (OLE) report. The trial was originally planned to continue until 813 primary endpoints had occurred, but after the protocol-specified second interim analysis on 6 May 2010, when a total of 501 adjudicated primary endpoint events were reviewed by the Data Safety Monitoring Committee (DSMC), the DSMC and the Executive Steering Committee (ESC) recommended that the study be stopped, based on pre-specified stopping rules in the study design regarding early attainment of positive efficacy results, and that all subjects be offered eplerenone. Consequently, enrolment into the study was stopped on 26 May 2010, and a 12 month open-label phase was added, where consenting subjects who were participating in the double-blind phase of the study were offered the opportunity to receive open-label eplerenone treatment once appropriate regulatory and ethics committee approvals had been obtained. Although enrolment into the study was halted on 26 May 2010, the double-blind phase of the study continued until all active patients were able to be transitioned into the OLE phase of the study. The OLE phase of the study was ongoing at the time of submission to the TGA.

All double-blind data collected from study start (30 March 2006) to 25 May 2010 were included in the initial primary CSR. However, since enrolled subjects continued in the double-blind phase after 25 May 2010, individual subject data were not unblinded in this initial primary CSR. After the complete transition of consenting patients into the OLE phase of the study and the double-blind phase had ended, subject-level data were released and the initial primary CSR was amended (this is the first of the 3 sets of CSRs submitted to the TGA, labelled as "amended pCSR"). All data from the double-blind phase collected after 25 May 2010 up until completion of the double-blind phase (18 March 2011) are reported in the supplemental CSR (sCSR). The sCSR reported efficacy and safety data on 2 datasets: double-blind data from termination of enrolment (26 May 2010) to end of double-blind phase (18 March 2011), and the complete

double-blind data from study initiation (30 March 2006) to end of double-blind phase (18 March 2011). All safety data collected in the OLE phase up to the submission cut-off point date of 14 June 2011 are reported in the OLE report. The content and scope of the three sets of CSRs included in this submission are summarised in Table 1 below.

Table 1. Summary of A6141079 clinical study reports included in TGA application

Clinical Study Report	Description	Period/Patients Covered
Amended Primary CSR (pCSR)	Efficacy and safety data from study initiation to termination of enrolment, including subject level data listings and serious adverse event narratives.	<i>Data from the double blind phase only (up to 25 May 2010)</i> Data for all subjects from study initiation (30 March 2006) to termination of enrolment (25 May 2010) ^a
Supplemental CSR	Summary of efficacy and safety data covering period from termination of enrollment to end of the double blind phase. Also includes a summary of the full double blind phase from study initiation to end of double blind phase.	<i>Data from the double blind phase only</i> Data for all subjects still in double blinded treatment from termination of enrolment (26 May 2010) to end of double blind phase (18 March 2011) ^a Also includes an overall summary of all double blind data from the double blind phase: from study initiation (30 March 2006) to end of double blind phase (18 March 2011) ^a
Open label extension (OLE) report	Interim analysis of available safety data from ongoing open label phase of study.	<i>Open Label period data only</i> Data from all subjects in OLE phase i.e. from end of their double blind phase to submission cut-off point (14 June 2011) ^b .

^a Does not include data from the OLE phase of subjects already enrolled in OLE.

^b Does not include data from the double blind phase of subjects in overlapping double blind phase.

In the sCSR, the efficacy data were summarised as descriptive statistics for each treatment group, and no p-values for treatment group comparisons were reported. The sponsor has stated that the OLE report submitted is an interim synopsis-type study report presenting a snapshot of the safety data from the OLE phase up to the submission cut-off point date of 14 June 2011. No efficacy analysis was done in the OLE phase, and only safety data was reported in the OLE report. The sponsor has also stated that in order to present the most current interim safety update for this submission, data cleaning of the OLE report was still ongoing when a database snapshot was made on 14 June 2011, and hence the database was not fully reconciled at the time of the data snapshot.

In this evaluation report, the amended pCSR will be evaluated as a pivotal efficacy study report. The sCSR will be summarised and presented below. The OLE report does not contain any efficacy analysis, and will be presented in the safety section of this report.

6.1.1. Pivotal efficacy study report

6.1.1.1. Study A6141079 (EMPHASIS-HF Study) amended pCSR: double-blind phase up to 25 May 2010

6.1.1.1.1. Study design, objectives, locations and dates

This was an international, multi-centre randomised, double-blind placebo-controlled, parallel-group trial. The primary objective of this trial was to evaluate the efficacy and safety of eplerenone plus standard HF therapy versus placebo plus standard HF therapy on the cumulative incidence of cardiovascular (CV) mortality or HF hospitalisation (a composite primary endpoint). Standard HF therapy included ACE-I and/or angiotensin II receptor blockers (ARB) and beta-blockers at the optimal target or maximally tolerated doses (unless contraindicated), and diuretics if clinically indicated to minimise fluid retention.

The study involved 357 centres in 29 countries¹. Study initiation and completion dates were 30 March 2006 to 25 May 2010 for this amended pCSR.

6.1.1.1.2. Inclusion and exclusion criteria

Subjects in the study were male or female of ≥ 55 years of age, with chronic systolic HF of either ischemic or non-ischemic aetiology and of duration of at least 4 weeks, with left ventricular ejection fraction [LVEF] $\leq 30\%$ or LVEF $\leq 35\%$ in addition to QRS duration ≥ 130 milliseconds (msec), with functional capacity of NYHA class II, and treated with ACE-Is and/or ARBs, beta-blockers, or diuretics. Subjects also needed to have serum potassium level ≤ 5.0 mmol/L and estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m² within 24 hours prior to randomisation. Randomisation should have occurred no later than 6 months from the date of admission to a hospital for a cardiovascular reason (or, in the absence of a recent admission to hospital for a cardiovascular reason, documentation of a plasma concentration of brain natriuretic peptide [BNP] of at least 250 pg/mL or amino-terminal pro-brain natriuretic peptide [NT-p-BNP] of at least 500 pg/mL for males and 750 pg/mL for females, within 15 days of randomisation).

The main exclusion criteria were: severe chronic systolic heart failure, defined as subjects who demonstrated symptoms at rest despite optimal medical therapy; myocardial infarction complicated by left ventricular systolic dysfunction and clinical heart failure, stroke, cardiac surgery or percutaneous coronary intervention within 30 days prior to randomisation; concomitant use of potent cytochrome p450 3A4 (CYP3A4) inhibitors, or CYP3A4 inducers.

Comments: The inclusion and exclusion criteria aimed to recruit a study population of adult patients ≥ 55 years of age with chronic heart failure and NYHA class II functional capacity, on standard HF medications, and reduced LVEF. The selection of patients with concomitant standard HF treatment is consistent with the TGA-adopted EMA guidelines on the clinical investigation of drugs for treatment of cardiac failure², and in keeping with the proposed indication. It is noted that although the inclusion criteria stated that subjects on ACE inhibitors, ARBs, or beta-blockers should be on optimal target or maximal tolerated dose, and that the sponsor has included a list of optimal target doses of ACE inhibitors, ARBs, and beta-blockers in Appendix 1 of the protocol, it was stated in the protocol that the optimal dose for each subject was decided by the investigator based on clinical judgment, taking into account tolerability and information from large randomised trials. Investigators were asked to attempt to optimise therapy for each individual subject, but no single dose of ACE inhibitor, ARB or beta-blocker was mandated. The use of clinical judgment to assess what constitutes optimal dose is appropriate as it is reflective of the clinical management of the target patient population, where optimal standard HF treatment will be based on clinical judgment of treating physician rather than a specified dose.

The restrictions on serum potassium level ≤ 5.0 mmol/L is consistent with the currently-approved Australian PI for eplerenone which stated that "*The principal risk of INSPRA is hyperkalaemia*" and that "*INSPRA should not be administered to patients with clinically significant hyperkalaemia (serum potassium >5.5 mmol/L at initiation)*". In the currently approved Australian PI for eplerenone, it is stated that "*INSPRA should not be administered to patients with moderate to severe renal insufficiency (creatinine clearance <50 mL/min)*". No rationale was given in the

¹ Argentina, Australia, Belgium, Canada, Czech Republic, France, Germany, Greece, China [Hong Kong], Hungary, India, Ireland, Italy, Korea, Mexico, Netherlands, Poland, Portugal, Russia, Singapore, Slovakia, South Africa, Spain, Sweden, Ukraine, United Arab Emirates, United Kingdom, United States, Venezuela

² European Agency for the Evaluation of Medicinal Products. Notes for guidance on clinical investigation of medicinal products for treatment of cardiac failure. 1999.

study report or study protocol for the inclusion criterion of eGFR \geq 30 mL/min/1.73 m² instead of \geq 50 mL/min/1.73 m². In the sponsor's Clinical Overview included with this submission, the sponsor has stated that "*This is the first large study with an aldosterone antagonist that included subjects with moderate renal impairment (eGFR 30 to 49 mL/min/1.73 m²). Unlike in the EPHESUS trial where patients were excluded with moderate renal impairment, the present study enrolled subjects with mild and moderate renal impairment.*" It appeared to the evaluator that the sponsor had meant that the inclusion of subjects with eGFR of 30 to 49 mL/min/1.73 m² was planned prospectively with the intention of evaluating the efficacy and safety in this group of patients. However, this was not clearly stated in the study protocol or study report, and was not included in the objective of the study. This will be raised as a clinical question (see Question under *Clinical Questions*)

The exclusion of concomitant use of CYP3A4 inhibitors and inducers is consistent with the known pharmacokinetics of eplerenone as described in the currently-approved Australian PI, that the metabolism of eplerenone is predominantly mediated via CYP3A4.

6.1.1.1.3. Study treatments

Subjects received 1 tablet of eplerenone 25 mg or matching placebo once daily (OD) for the first 4 weeks of treatment. For subjects with an eGFR between 30 and 49 mL/min/1.73 m², the initial dose of eplerenone was 25 mg or matching placebo (1 tablet) once every other day (EOD) for the first 4 weeks of treatment. The first dose of study drug was to be taken at randomisation. All subsequent doses of study drug were to be taken orally each morning with water and with or without food.

At Week 1 following randomisation, the dose of study drug could be adjusted according to serum potassium level. At 4 weeks and at each subsequent clinic visit, the serum potassium level was to be checked, and the study drug dose was to be adjusted accordingly. Serum potassium level was also checked 1 week after any dose adjustment. For subjects with an eGFR between 30 to 49 mL/min/1.73 m², the maximum daily dose of eplerenone was not to exceed 25 mg.

Comments: The starting dose of eplerenone and the subsequent titration schedule according to serum potassium levels for subjects with eGFR \geq 50 mL/min/1.73 m² are appropriate and consistent with the dosing recommendation in the currently-approved Australian PI for eplerenone. However, the rationale for the dosing regimen for subjects with eGFR between 30 to 49 mL/min/1.73 m² was not given. The only references to dosing in patients with renal impairment in the currently-approved PI are that "INSPIRA should not be administered to patients with moderate to severe renal insufficiency (creatinine clearance $<$ 50mL/min)", that "*No initial dose adjustment is required in patients with mild renal impairment*" and that "*INSPIRA is contraindicated in patients with severe renal insufficiency*". This will be raised as a clinical question (see Clinical Questions below).

6.1.1.1.4. Efficacy variables and outcomes

The primary efficacy endpoint (composite endpoint) was the first occurrence of cardiovascular (CV) mortality or heart failure (HF) hospitalisation. CV mortality was defined as death due to HF, myocardial infarction (MI), cardiac arrhythmia, stroke, or other CV cause (such as aneurysm or pulmonary embolism). Hospitalisation for HF was defined as an overnight stay or longer, in a hospital environment (emergency room, observation unit or in-patient care, or similar facility including admission to a day care facility) with a discharge diagnosis that included a CV reason for hospitalisation.

The main secondary efficacy endpoint was the composite endpoint of first occurrence of all-cause mortality or HF hospitalisation. Other secondary endpoints included first occurrence of all-cause mortality, CV mortality, all-cause hospitalisation, HF hospitalisation, all-cause mortality or all-cause hospitalisation, HF mortality or HF hospitalisation, CV hospitalisation, fatal/nonfatal MI, fatal/nonfatal stroke, implantation of cardiac defibrillator (ICD), implantation of cardiac resynchronization therapy (CRT) device, new-onset atrial fibrillation (AF)/flutter, new-onset diabetes mellitus (DM), worsening renal function (if it results in hospitalisation), and hospitalisation for hyperkalemia.

At each study visit or follow-up contact, subjects were questioned specifically (by using targeted prompts) regarding clinical endpoints. All primary and secondary endpoints were adjudicated by an independent blinded Endpoint Adjudication Committee, except for new onset of DM and new onset of AF/flutter, which were reported by the study site directly.

Comments: The TGA-adopted EMA guidelines on the clinical investigation of drugs for treatment of cardiac failure³ recommend that the preferred primary endpoint of heart failure treatment studies be all-cause mortality, but that “provided that a deleterious effect on mortality is ruled out, improvement in symptoms and correlation of haemodynamic improvement with clinical findings can be accepted as evidence of efficacy”. This is based on the principle that the main objectives are to demonstrate improvement in cardiovascular morbidity or clinical symptoms, and no adverse effect on overall mortality. The recommended secondary endpoints include cardiac and non-cardiac deaths, and hospitalisations. Although the study primary endpoint differs from the recommended preferred primary endpoint of all-cause mortality, it allows a composite assessment of effect on CV mortality and HF morbidity (as assessed by HF hospitalisation). The main secondary endpoint allows composite assessment of effect on all-cause mortality and HF morbidity. The other secondary endpoints evaluated separately mortality endpoints (all-cause, CV and HF deaths) and morbidity endpoints (all-cause, CV and HF hospitalisation), as well as the composite endpoint of HF mortality and HF morbidity (as assessed by HF hospitalisation). Overall, the study endpoints allowed evaluation of the effect of eplerenone on all-cause mortality and CV morbidity.

6.1.1.1.5. Randomisation and blinding methods

Subjects were randomised in a 1:1 ratio to receive double-blind study drug in the order in which they met the criteria for randomisation, according to a computer-generated randomisation schedule prepared by the sponsor prior to the start of the trial. The study drug and placebo for the double-blind phase were similar in size, color, smell, taste, and appearance. The Endpoint Adjudication Committee which adjudicated the clinical endpoints was blinded. An independent Data Safety Monitoring Committee (DSMC), which was not otherwise involved in the conduct of the trial, reviewed unblinded data and provided recommendations to the steering committee regarding the conduct and early termination of the trial.

6.1.1.1.6. Analysis populations

Efficacy analyses were performed on the Full Analysis Set (FAS), which was composed of all randomised subjects. For all efficacy analyses during the double-blind phase, available data from the FAS was analysed according to the intent-to-treat (ITT) principle based on the subjects' randomised treatment assignment, regardless of compliance with the study drug and the protocol. Therefore, the efficacy analysis datasets in the double-blind phase included all available study endpoints from all randomised subjects, irrespective of any deviations from the protocol or premature discontinuation of study drug.

³<http://www.tga.gov.au/pdf/euguide/ewp023595en.pdf>

Comments: Analysis in the ITT population is appropriate and is in keeping with the TGA-adopted ICH E 9 Statistical Principles for Clinical Trials.⁴

6.1.1.1.7. Sample size

This was an endpoint-driven study. It had been estimated that a total of 813 primary endpoint events were needed in order to have at least 80% power to detect an 18% risk reduction in the primary efficacy endpoint. This was based on the 2-sided log-rank test for the between-treatment comparison in the time to first occurrence of CV mortality or hospitalisation for HF (that is, the primary efficacy endpoint) at a 5% level of significance. There were 2 planned interim analyses. Based on a blinded data review on 28 March 2009, the estimated annual event rate (2 treatments combined) was 12%, which was lower than the original estimate of 18%, and the enrolment rate was approximately 50 to 60 subjects per month. It was then estimated that in order to reach the 813 primary endpoints required for trial completion, the study would require a sample size of approximately 3100 subjects (1550 per treatment arm) and an estimated enrolment period of 54 months and study duration of approximately 60 months. However, the enrolment for the double-blind phase of the trial was subsequently stopped on 26 May 2010 based on the recommendation of the DSMC and the ESC, as previously described.

6.1.1.1.8. Statistical methods

The primary statistical analysis model for the double-blind phase was determined as the Cox proportional hazards (PH) regression model adjusting for baseline prognostic factors based on the Full Analysis Set⁵. All prespecified primary and secondary efficacy endpoints for the double-blind phase were analysed using this adjusted Cox PH model. Results were considered statistically significant if a p-value <0.049 (adjusted for interim analyses) was obtained for the primary endpoint and <0.01 for the secondary endpoints. When statistically significant results were found for composite endpoints, the results were broken down by each component of the composite endpoint in order to ascertain which components were contributing to the statistical significance.

The primary efficacy analysis was to evaluate the treatment effect in time to the first occurrence of CV mortality or HF hospitalisation. The hazard ratio of the eplerenone group to the placebo group and its corresponding 95% confidence intervals (CIs) were provided. A Kaplan-Meier curve for the cumulative probability of the primary endpoint event rate was generated by each treatment group based on the log-rank test. All of the time-to-event secondary endpoints were analysed using the same statistical methods described above for the primary endpoint.

In addition, prespecified subgroups⁶ were analysed for the primary endpoint during the double-blind phase using an univariate Cox PH model including treatment as the only factor, without any covariate adjustment. Hazard ratios and 95% CIs were obtained from the Cox PH model. The treatment-by-subgroup interaction was evaluated using a Cox PH model with terms for treatment, subgroup, and interactions between treatment and subgroup.

The sponsor has stated that in order to fulfil a European post-approval commitment issued at the time of approval on 10 March 2004, efficacy and safety analyses were also conducted during

⁴ <http://www.tga.gov.au/pdf/euguide/ich036396en.pdf>

⁵ The baseline prognostic factors were age, eGFR, left ventricular ejection fraction, body mass index, haemoglobin, heart rate, systolic blood pressure, diabetes, history of hypertension, prior MI, baseline left bundle branch block (LBBB) or baseline QRS >130 msec, and AF.

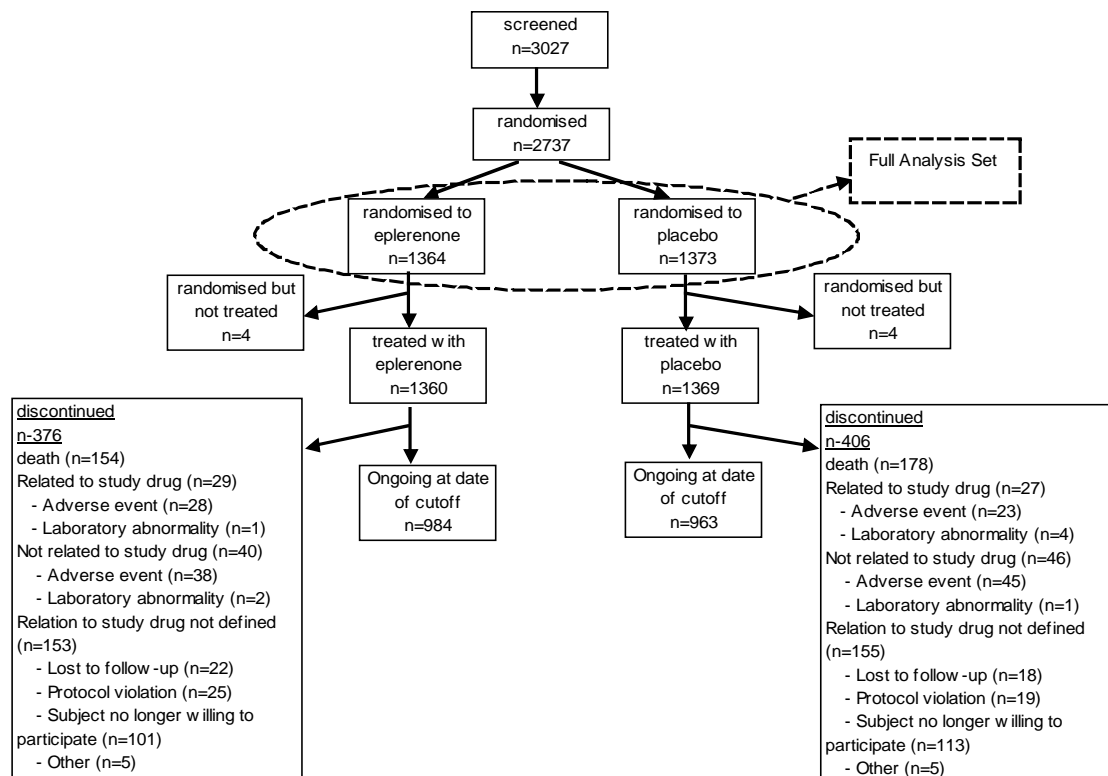
⁶ The specified subgroups were: Gender (male and female), Age (<65 and ≥65), Region (Western Europe/Australia, Eastern Europe, Asia/Middle East/Africa, and South/North America), Baseline SBP (<median and ≥median), Baseline pulse pressure (<median and ≥median), Baseline HR (<median and ≥median), Baseline eGFR <60 mL/min/1.73m² and ≥60 mL/min/1.73m², Baseline NYHA Class (I and II combined, and III and IV combined), Baseline etiology of HF (ischemic and nonischemic heart failure), Prior beta-blocker plus ACE inhibitor plus ARB use (yes and no), Prior beta-blocker use (yes and no), Prior ACE inhibitor or ARB use (yes and no), LVEF (<30% and ≥30%), AF (yes and no), Diabetes (yes and no), History of hypertension (yes and no), Prior hospitalisation (<180 days and ≥180 days), Prior CRT or ICD procedures (yes and no), QRS>130 msec (yes and no), LBBB (yes and no)

this study for the “very elderly” subjects in this study (age ≥ 75 years) in the Full Analysis Set. In addition, the subgroup of subjects who were < 75 years of age was also analysed. The sponsor has stated that the full results of the post-approval commitment analyses will be presented in a separate study report.

6.1.1.1.9. Participant flow

A total of 3027 subjects were screened, and 2737 subjects were randomised: 1364 to eplerenone group and 1373 to placebo group (see flow chart below).

Figure 1. Participant flow



All subjects who were randomised were included in the FAS (1364 and 1373 subjects in the eplerenone and placebo groups, respectively).

6.1.1.1.10. Major protocol violations/deviations

The most common protocol deviations involved 13 subjects at different sites who were randomised with the same randomisation assignment as another subject. In addition, the list containing the unblinding information for 12 subjects was accidentally sent to the site pharmacy. Ten subjects also did not initially sign the informed consent form and 6 subjects were dispensed the incorrect study drug from another randomisation assignment. The sponsor did not provide information regarding the number of subjects in each treatment group with each category of protocol deviations.

The sponsor has stated that none of the protocol deviations were believed to have affected the conduct of the study or the integrity of the study data. With regards to the 13 subjects who were erroneously given the same randomisation number, the sponsor has stated that the site numbers were different and as these were part of the subject identification numbers, there had been no difficulty in identifying these patients, and hence this error had no impact on the outcome of the study. With regards to the 12 subjects whose unblinding information was accidentally sent to the site pharmacy, the sponsor stated that the incident was independently judged by the ESC and the DSMC as having no impact on trial outcome because no personnel with direct responsibility for any subject were inappropriately exposed to any study documents.

In addition, only adjudicated endpoint events were used in efficacy analyses, and these were adjudicated in a blinded manner by an independent endpoint adjudication committee whose members were not investigators. With regards to the subjects who did not initially sign their informed consent, these subjects did so prior to dosing once the error was detected.

Comments: The rationale for the conclusion that the stated protocol deviations did not affect the integrity of the study data is reasonable. The sponsor did not provide information regarding the number of subjects in each treatment group with each category of protocol deviations, which would be important to assess whether the incidence of protocol deviations was comparable between treatment groups. This will be raised as a clinical question (see Question 3 under *Clinical Questions*)

6.1.1.1.11. Baseline data

The baseline demographic and disease characteristics were comparable between treatment groups. The majority of subjects in each treatment group were male (77.3% [1055/1364] and 78.1% [1072/1373] in eplerenone and placebo groups, respectively), and White (82.6% [1127/1364] and 83.1% [1141/1373], respectively). The mean ((SD) age was 68.7 (7.7) and 68.6 (7.6), respectively. The aetiology of HF in the majority of subjects was ischaemic (69.7% [951/1364] and 68.1% [935/1373], respectively). The mean duration of ischaemic HF was 5.36 years and 5.34 years, respectively.

Baseline co-existing medical conditions were comparable between treatment groups. A summary of co-existing medical conditions in $\geq 10\%$ of subjects at screening in either treatment group was provided. Overall, 80%, 24%, 90% and 89%⁷ of the patients received ACEIs, angiotension II antagonists, beta-blockers and diuretics, respectively and the number of subjects on ACE-Is, ARBs, and beta blockers were comparable between treatment groups.

Comments: Overall, the baseline demographic and disease characteristics were comparable between treatment groups. The median age was not presented in the amended pCSR, but a look through the subgroup analysis results showed that there were 883 subjects aged < 65 years and 1654 subjects aged ≥ 65 years who were evaluated for the subgroup analyses. Ischaemic aetiology accounts for over 50% of new CHF cases in Australia⁸, and the incidence of CHF in Australia, as in other developed countries, increases with age. The study population, with a mean age of about 69 years, a mainly ischemic aetiology of HF and with majority of patients on ACEIs, beta-blockers and/ or diuretics was reflective of the targeted clinical HF patient population.

6.1.1.1.12. Results for the primary efficacy outcome

The primary efficacy endpoint was the first occurrence of CV mortality or hospitalisation for HF. The primary efficacy outcome was analysed in the Full Analysis Set population. Overall, of 18.3% (249/1364) of subjects in the eplerenone group and 25.9% (356/1373) of subjects in the placebo group reported having CV mortality or hospitalisation for HF. This represents a 37.0% relative risk reduction for the eplerenone group compared to the placebo group and this was found to be statistically significant ($p < 0.0001$).

The results were statistically significant in favour of eplerenone for the component of hospitalisation for HF, but not for the component of CV mortality⁹. Hospitalisation for HF occurred in 12.0% (164/1364) of subjects in the eplerenone group and 18.4% (253/1373) of subjects in the placebo group. This represents a 42.4% relative risk reduction for the

⁷ Sponsor comment: "78%, 19%, 87% and 84%."

⁸ Australian Institute of Health and Welfare (AIHW) and the National Heart Foundation of Australia (NHFA). Heart, stroke and vascular diseases—Australian facts 2004.

⁹ The components were analysed as secondary endpoints. In accordance with the Statistical Analysis Plan, secondary endpoint analysis results were considered statistically significant if a p-value < 0.01 was obtained.

eplerenone group compared to the placebo group ($p < 0.0001$). CV mortality occurred in 10.8% (147/1364) of subjects in the eplerenone group and 13.5% (185/1373) of subjects in the placebo group, representing a 24.3% relative risk reduction for the eplerenone group compared to the placebo group ($p = 0.0120$).

Kaplan-Meier plots of time to first event for the primary endpoint and its components were presented.

6.1.1.1.13. Results for other efficacy outcomes

Analysis of the main secondary efficacy endpoint of the first occurrence of all-cause mortality or HF hospitalisation was statistically significant in favour of eplerenone, occurring in 19.8% (270/1364) of subjects in the eplerenone group and 27.4% (376/1373) of subjects in the placebo group, representing a 35.3% relative risk reduction for the eplerenone group compared to the placebo group ($p < 0.0001$).

Analyses of the other secondary efficacy endpoints showed that there was a statistically significant relative risk reduction for the eplerenone group compared to the placebo group for the secondary endpoints of all-cause mortality, all-cause hospitalisation, HF hospitalisation, all-cause death or all-cause hospitalisation, HF death or HF hospitalisation, and CV hospitalisation. Kaplan-Meier plots of time to first event of all-cause hospitalisation and of all-cause death were also presented.

Subgroup analyses¹⁰ on the primary endpoint showed that there was a statistically significant difference between eplerenone and placebo (in favour of eplerenone) for each subgroup, except for the subgroups of subjects without prior beta-blocker use, subjects without prior ACE or ARB use, subjects with prior hospitalisation ≥ 180 days, and subjects with baseline LBBB present. There were no significant treatment-by-subgroup interactions for the primary endpoint survival analysis using the Wald test for any subgroups analysed.

Subgroup analyses of the main secondary endpoint of the first occurrence of all-cause mortality or HF hospitalisation showed that there was a statistically significant difference between eplerenone and placebo (in favour of eplerenone) for each subgroup, except for the subgroups of subjects with non-ischaemic HF, subjects with prior beta-blocker plus ACE-I plus ARB use, subjects without prior beta-blocker use, subjects without prior ACE-I or ARB use, subjects with baseline LVEF $\geq 30\%$, subjects with prior hospitalisation ≥ 180 days, subjects with baseline QRS > 130 msec, subjects with baseline LBBB present, and subjects in all the regions except Asia/Middle East/Africa.

Subgroup analyses of secondary endpoints of fatal/nonfatal MI, fatal/nonfatal stroke, implantation of cardiac defibrillator, implantation of a CRT, worsening renal function (if it results in hospitalisation), hospitalisation for hyperkalemia, new-onset AF, and new-onset DM showed that there was no statistically significant difference between treatment groups in all subgroups, consistent with the results in the overall study population for these endpoints. Subgroup analyses of the remaining secondary endpoints were presented and showed that for mortality endpoints of all-cause death and CV death, subgroup analyses yielded results that were not statistically significant across all subgroups except for subjects of age < 75 years, subjects with prior beta-blocker use, and subjects with LVEF $< 30\%$. Analyses suggested that there was greater risk in eplerenone group compared to placebo group of all-cause death, and of CV death, in subjects with no prior beta-blocker use and in subjects with no prior ACE-I or ARB use, but these results were not statistically significant. There also appeared to be a greater risk in eplerenone group compared to placebo group of all-cause death, in subjects with prior hospitalisation of ≥ 180 days, but again the results were not statistically significant.

¹⁰ The subgroup of NYHA class III and IV had a sample size of only $n=3$, and no meaningful analysis or interpretation could be done in this subgroup

Subgroup analyses of the morbidity endpoints of all-cause hospitalisation, HF hospitalisation and CV hospitalisation yielded results that were statistically significant in favour of eplerenone in some subgroups, and not statistically significant in others. There was no obvious pattern indicating that eplerenone was definitively less effective in certain subgroups across the morbidity secondary endpoints, except for the subgroup of subjects with prior beta-blocker plus ACE-I plus ARB use, subjects without prior beta-blocker use, and subjects with baseline LBBB present.

Comments on efficacy results in the double-blind phase up to 25 May 2010 (amended pCSR):
The efficacy results of the primary efficacy endpoint, the main secondary efficacy endpoints, and the main mortality and morbidity secondary endpoints are summarised in Table 2 below.

Table 2. Summary of efficacy results of primary efficacy endpoint and main secondary efficacy endpoints, full analysis set population

	Relative risk reduction (eplerenone compared to placebo)	p- value *
Primary efficacy endpoint - CV mortality or hospitalisation for HF	37.0%	< 0.0001
Main secondary efficacy - all-cause mortality or HF hospitalisation	35.3%	< 0.0001
Mortality secondary endpoints		
All-cause mortality	23.9%	0.0081
CV mortality	<u>24.3%</u>	<u>0.0120</u>
Morbidity secondary endpoints		
All-cause hospitalisation	23.2%	< 0.0001
HF hospitalisation	42.4%	< 0.0001
CV hospitalisation	30.6%	< 0.0001
All-cause mortality-morbidity composite secondary endpoint		
All-cause mortality or all-cause hospitalisation	24.9%	< 0.0001
HF mortality-morbidity composite secondary endpoint		
HF mortality or HF hospitalisation	42.3%	< 0.0001

*Results are statistically significant if $p < 0.049$ for primary endpoint and $p < 0.01$ for all secondary endpoints. CV= cardiovascular; HF= heart failure

Figures in blue and underlined are not statistically significant.

Overall, the results showed that there were statistically significant relative risk reductions for eplerenone compared to placebo for both all-cause mortality as well as CV and HF morbidity (as assessed by CV and HF hospitalisations). Although the difference in CV mortality between treatment groups was not statistically significant, there was a relative risk reduction of 24.3% in favour of eplerenone, and the p-value was close to the level of significance ($p=0.0120$).

Although analyses of the secondary endpoints of fatal/nonfatal MI, fatal/nonfatal stroke, implantation of cardiac defibrillator, and implantation of a CRT showed that there were no statistically significant differences between treatment groups, it is noted that the number of patients with these secondary endpoints were small in either treatment group, making analysis and interpretation difficult. Analyses of the secondary endpoints

of hospitalisation for worsening renal function, and hospitalisation for hyperkalemia did not show statistically significant higher incidences in the eplerenone group compared to the placebo group, but interpretation was confounded by the small number of patients with these secondary endpoints in either treatment group.

Subgroup analyses on the primary endpoint showed that there was a statistically significant relative risk reduction in favour of eplerenone over placebo across the subgroups, except for the subgroups of subjects without prior beta-blocker use, subjects without prior ACE or ARB use, subjects with prior hospitalisation ≥ 180 days, and subjects with baseline LBBB present (See Figure 2 below). However, the sample sizes in these subgroups were small, making interpretation difficult. In addition, there were no significant treatment-by-subgroup interactions for the primary endpoint survival analysis using the Wald test for any subgroups analysed.

Figure 2. Subgroup analyses of the primary endpoint (heart failure hospitalisation or cardiovascular death) (full analysis set), study A6141079, double-blind phase up to 25 May 2010

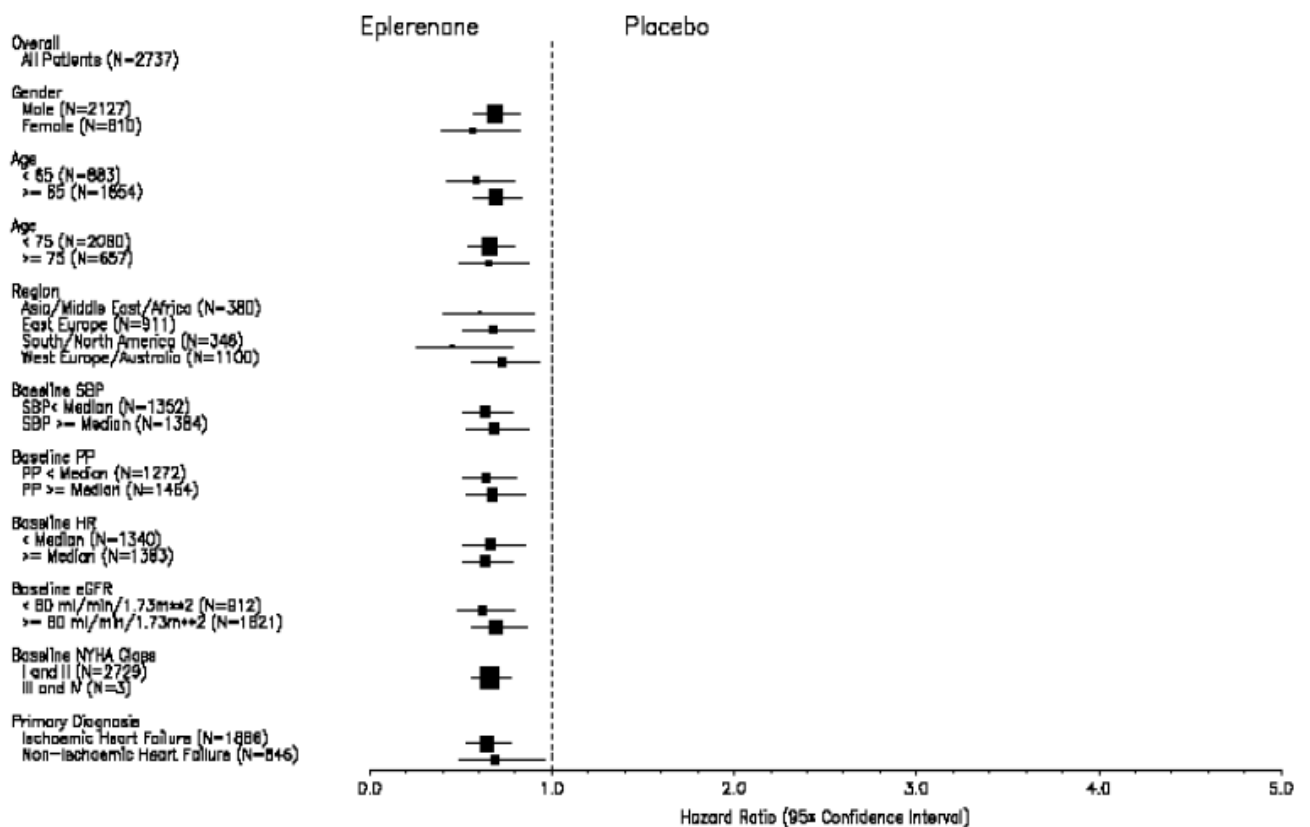
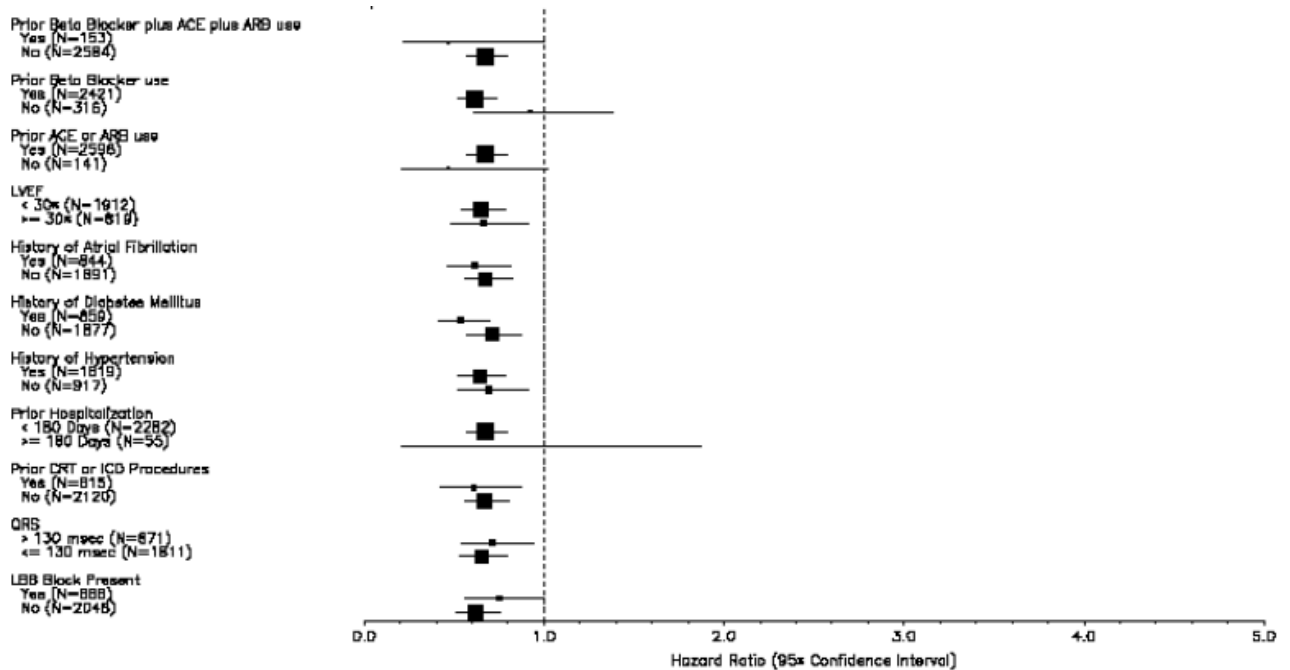


Figure 2 continued. Subgroup analyses of the primary endpoint (heart failure hospitalisation or cardiovascular death) (full analysis set), study A6141079, double-blind phase up to 25 May 2010



SBP = systolic blood pressure; PP = pulse pressure; HR = heart rate; eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; LVEF = left ventricular ejection fraction; CRT = cardiac resynchronization therapy; ICD = implantation of cardiac defibrillator; QRS = time from electrocardiogram Q wave to the end of the S wave corresponding to ventricle depolarization; LBB = left bundle branch

In addition, a look through the subgroup analyses on the secondary endpoints showed that there was no obvious pattern indicating that eplerenone was definitively less effective in certain subgroups across the endpoints, except the subgroups of subjects with prior beta-blocker plus ACE-I plus ARB use, subjects without prior beta-blocker use, subjects without prior ACE-I or ARB use, subjects with baseline LBBB, and subjects with prior hospitalisation of ≥ 180 days. However, it is noted that the sample size in these subgroups were all small, except for that of subjects with baseline LBBB (n=153 for the subgroup with prior beta-blocker plus ACE-I plus ARB use; n=316 for subgroup without prior beta-blocker use; n=141 for the subgroup without prior ACE-I or ARB use respectively; n=55 for the subgroup with prior hospitalisation of ≥ 180 days), making interpretation difficult. There were 888 subjects¹¹ in the subgroup of subjects with baseline LBBB. The sponsor did not put forward any postulation to explain the lack of efficacy in this particular subgroup of subjects with baseline LBBB. However, it is noted that analyses in the subgroup of subjects with baseline QRS > 130 msec (n=871) showed statistically significant relative risk reduction for eplerenone over placebo for the morbidity endpoints of all-cause hospitalisation and CV hospitalisation.

Subgroup analyses of the mortality endpoints of all-cause death and CV death showed that there was no statistically significant greater risk of all-cause or CV mortality in the eplerenone group compared to placebo across the subgroups.

¹¹ Sponsor correction: 688 subjects.

6.1.1.2. Other efficacy reports

6.1.1.3. Study A6141079 (EMPHASIS-HF): supplementary CSR

The supplemental CSR (sCSR) presented efficacy data for 2 datasets: all data collected from 26 May 2010 to the end of the double-blind phase (18 March 2011), referred to in the sCSR as the “post-cut off dataset”, and the complete double-blind-phase data (from 30 March 2006 to 18 March 2011), referred to in the sCSR as the “complete double-blind phase dataset”.

A summary of subject disposition for the post-cutoff dataset was presented in the submission.

A total of 1041 subjects were randomised to the eplerenone group, and 1006 subjects to the placebo group. Of 922 subjects treated with eplerenone after the cut-off date, 812 (78.0%) completed the double-blind phase. Of 889 subjects treated with placebo, 759 (75.4%) completed the double-blind phase. A summary of subject disposition for the complete double-blind phase dataset was presented. A total of 1367 subjects were randomised to the eplerenone group, and 1376 subjects to the placebo group. Of 1364 subjects treated with eplerenone, 826 (60.4%) completed the double-blind phase. Of 1372 subjects treated with placebo, 771 (56.0%) completed the double-blind phase.

Efficacy analyses in the post-cutoff dataset and in the complete double-blind phase dataset were performed in the Full Analysis Set, which comprised of all subjects who were assigned to study treatment (i.e. all randomised subjects). The analysis populations for the post-cut-off dataset and the complete double-blind phase dataset were presented in the submission.

In both the post-cutoff dataset and the complete double-blind phase dataset, the baseline demographic and disease characteristics were comparable between treatment groups. In both datasets, the majority of subjects in each treatment group were male (post-cut off dataset: 76.4% [795/1041] and 78.2% [787/1006] in eplerenone and placebo groups, respectively; complete double-blind phase dataset: 77.4% [1058/1367] and 78.1% [1074/1376], respectively), and White (post-cut off dataset: 85.0% [885/1041] and 84.8% [853/1006], respectively; complete double-blind phase dataset: 82.6% [1129/1367] and 83.1% [1143/1376], respectively). In the post-cut off dataset, the mean (SD) age was 68.3 (7.5) and 68.3 (7.7) in eplerenone and placebo groups, respectively, and that in the complete double-blind phase dataset was 68.7 (7.7) and 68.6 (7.6), respectively. In the post-cut off dataset, the aetiology of HF in the majority of subjects was ischaemic (67.4% [702/1041] and 66.9% [673/1006], respectively), and the mean duration of ischaemic HF was 5.31 years and 5.15 years, respectively. The proportion of subjects with ischaemic HF and mean duration of ischaemic HF for the complete double-blind phase dataset was not provided in the sCSR.

In the post-cut off dataset, baseline co-existing medical conditions were comparable between treatment groups. A summary of present medical conditions in $\geq 10\%$ of subjects at screening in either treatment group was provided in the submission. The number of subjects on ACE-Is, ARBs, and beta blockers were also comparable between treatment groups.

Analyses on the primary endpoint (occurrence of either CV death or hospitalisation for HF) in the post-cut off dataset and the complete double-blind phase dataset were presented in the submission. In the post-cut off dataset 3.6% (37/1041) of subjects in the eplerenone group met the primary endpoint (CV mortality or HF hospitalisation) compared to 3.4% (34/1006) of subjects in the placebo group. CV mortality occurred in 2.8% of subjects (29/1041) in the eplerenone group and 3.0% of subjects (30/1006) in the placebo group, while HF hospitalisation occurred in 2.1% of subjects (22/1041) in the eplerenone group and 2.1% of subjects (21/1006) in the placebo group. In the complete double-blind phase dataset 21.1% (288/1367) of subjects in the eplerenone group met the primary endpoint compared to 28.5% (392/1376) of subjects in the placebo group. CV mortality occurred in 13.0% of subjects (178/1367) in the eplerenone group and 15.6% of subjects (215/1376) in the placebo group, while HF hospitalisation occurred in 13.6% of subjects (186/1367) in the eplerenone group and

20.1% of subjects (277/1376) in the placebo group. The data were not analysed for statistical significance in the sCSR.

Analyses on the secondary endpoints in the post-cut off dataset and the complete double-blind phase dataset were presented in the sponsor's submission. In the post-cut off dataset, the incidence of all secondary endpoints was lower in the eplerenone group than in the placebo group, except for the composite endpoint of HF death or HF hospitalisation (0.9% and 0.6%¹² in the eplerenone and placebo groups, respectively), new-onset atrial fibrillation/flutter (0.9% and 0.6%¹³ in the eplerenone and placebo groups, respectively) and new-onset DM (0.7% in both the eplerenone and placebo groups, respectively). In the complete double-blind phase, the incidence of all secondary endpoints was lower in the eplerenone group than in the placebo group, except for fatal/non-fatal MI (3.6% and 2.9% in the eplerenone and placebo groups, respectively), hospitalisation for worsening renal function (0.7% in both the eplerenone and placebo groups, respectively) and hospitalisation for hyperkalemia (0.3% and 0.2% in the eplerenone and placebo groups, respectively). The data were not analysed for statistical significance in the sCSR.

Comments: Overall, the baseline demographic and disease characteristics were comparable between treatment groups in both the post-cut off dataset and the complete double-blind phase dataset, and were also comparable to those presented for the double-blind phase up to 25 May 2010. Although the efficacy results were not analysed for statistical significance, the results of the complete double-blind phase were generally comparable to those of the double-blind phase up to 25 May 2010.

Table 3. Baseline demographic and disease characteristics, and main efficacy endpoints for double-blind phase up to 25 May 2010, post-cut off dataset, and complete double-blind phase dataset

	Double-blind phase up to 25 May 2010		Post-cut off dataset		Complete double-blind phase dataset	
	Eplerenone N=1364	Placebo N=1373	Eplerenone N=1041	Placebo N=1006	Eplerenone N=1367	placebo N=1376
Baseline demographic and disease characteristics						
Males (%)	77.3	78.1	76.4	78.2	77.4	78.1
White (%)	82.6	83.1	85.0	84.8	82.6	83.1
Mean age (SD) (years)	68.7 (7.7)	68.6 (7.6)	68.3 (7.5)	68.3 (7.7)	68.7 (7.7)	68.6 (7.6)
Ischaemic aetiology of HF (%)	69.7	68.1	67.4	66.9	NA	NA
Mean duration of ischaemic HF (years)	5.36	5.34	5.31	5.15	NA	NA

¹² Sponsor comment: 2.3% and 2.2%.

¹³ Sponsor comment: 0.9% and 0.6%.

Primary efficacy endpoint - CV mortality or hospitalisation for HF	18.3%	25.9%	3.6%	3.4%	21.1%	28.5%
Main secondary efficacy - all-cause mortality or HF hospitalisation	19.8%	27.4%	3.7%	4.0%	22.8%	30.4%
Mortality secondary endpoints						
All-cause mortality	12.5%	15.5%	3.1%	4.0%	15.0%	18.4%
CV mortality	10.8%	13.5%	2.8%	3.0%	13.0%	15.6%
Morbidity secondary endpoints						
All-cause hospitalisation	29.9%	35.8%	4.5%	5.3%	33.9%	40.1%
HF hospitalisation	12.0%	18.4%	2.1%	2.1%	13.6%	20.1%
CV hospitalisation	22.3%	29.1%	3.5%	3.7%	25.3%	31.9%
All-cause mortality-morbidity composite secondary endpoint						
All-cause mortality or all-cause hospitalisation	33.9%	41.4%	5.6%	6.0%	38.8%	46.2%
HF mortality-morbidity composite secondary endpoint						
HF mortality or HF hospitalisation	12.5%	19.1%	2.3%	2.2%	14.2%	20.9%

CV= cardiovascular; HF= heart failure, NA= not available

6.2. Evaluator's conclusions on clinical efficacy for the proposed additional indication

Of reducing the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II heart failure and left ventricular systolic dysfunction in addition to standard optimal therapy.

Overall, the study design and study inclusion and exclusion criteria were appropriate and consistent with the TGA-adopted EMA guidelines on the clinical investigation of drugs for treatment of cardiac failure, and aimed to recruit a study population of adult patients ≥ 55 years of age with chronic heart failure and NYHA class II functional capacity, on standard HF medications, and reduced LVEF. The selection of patients with concomitant standard HF treatment is consistent with the TGA-adopted EMA guidelines on the clinical investigation of drugs for treatment of cardiac failure³, and in keeping with the proposed indication. However, no rationale was given for why patients with $eGFR \geq 30$ mL/min/1.73 m², were included when the currently-approved Australian PI for eplerenone stated that "INSPIRA should not be administered to patients with moderate to severe renal insufficiency (creatinine clearance < 50 mL/min)". In the sponsor's Clinical Overview included with this submission, the sponsor has stated that "This is the first large study with an aldosterone antagonist that included subjects with moderate renal impairment ($eGFR$ 30 to 49 mL/min/1.73 m²). Unlike in the EPHESUS trial where patients were excluded with moderate renal impairment, the present study enrolled subjects with mild and moderate renal impairment." It appeared to the evaluator that the sponsor had meant that the inclusion of subjects with $eGFR$ of 30 to 49 mL/min/1.73 m² was planned prospectively with the intention of evaluating the efficacy and safety in this group of patients. However, this was not clearly stated in the study protocol or study report, and was not included in the objective of the study.

The starting dose of eplerenone and the subsequent titration schedule according to serum potassium levels for subjects with $eGFR \geq 50$ mL/min/1.73 m² are appropriate and consistent with the dosing recommendation in the currently-approved PI for eplerenone. However, the rationale for the dosing regimen for subjects with $eGFR$ between 30 to 49 mL/min/1.73 m² was not given.

The primary and secondary efficacy endpoints were appropriate. The TGA-adopted EMA guidelines on the clinical investigation of drugs for treatment of cardiac failure³ recommend that the preferred primary endpoint of heart failure treatment studies be all-cause mortality, but that "provided that a deleterious effect on mortality is ruled out, improvement in symptoms and correlation of haemodynamic improvement with clinical findings can be accepted as evidence of efficacy". This is based on the principle that that main objectives are to demonstrate improvement in cardiovascular morbidity and clinical symptoms, and no adverse effect on overall mortality. Although the study primary endpoint differs from the recommended preferred primary endpoint of all-cause mortality, it allows a composite assessment of effect on CV mortality and HF morbidity (as assessed by HF hospitalisation). The secondary endpoints allowed composite assessment of effect on all-cause mortality and HF morbidity as well as individual mortality endpoints (all-cause, CV and HF deaths) and morbidity endpoints (all-cause, CV and HF hospitalisation). Together with the primary endpoint, these allow evaluation of whether there would be improvement in cardiovascular morbidity with no adverse effect on overall mortality of eplerenone compared to placebo.

In the double-blind phase data up to 25 May 2010, the baseline demographic and disease characteristics were comparable between treatment groups. The study population, with a mean age of about 69 years and where the aetiology of HF was mainly ischaemic, was reflective of the targeted clinical HF patient population. The baseline demographic and disease characteristics in the post-cut off dataset and the complete double-blind phase dataset were also comparable between treatment groups, as well as comparable to those presented for the double-blind phase up to 25 May 2010.

Overall, in the double-blind phase data up to 25 May 2010, efficacy analysis results showed a 37% relative risk reduction in the incidence of the primary composite endpoint of CV mortality or hospitalisation for HF in the eplerenone group compared to the placebo group, and this reduction was found to be statistically significant at $p < 0.0001$. The results also showed that there was a statistically significant relative risk reduction of 23.9% in all-cause mortality for eplerenone compared to placebo, as well as statistically significant relative risk reductions of 42% in hospitalisation for HF and of 31% in CV hospitalisation for eplerenone compared to placebo. Although the difference in CV mortality between treatment groups was not statistically significant, there was a relative risk reduction of 24.3% in favour of eplerenone, and the p-value was close to the level of significance ($p=0.0120$). Analyses in the complete double-blind phase dataset were consistent with the results in the amended pCSR.

Subgroup analyses of the mortality endpoints of all-cause death and CV death showed that there was no statistically significant greater risk of all-cause or CV mortality in the eplerenone group compared to placebo across the subgroups. Subgroup analyses of the morbidity endpoints showed that there was no obvious pattern indicating that eplerenone was definitively less effective in certain subgroups across the endpoints, except for the subgroups of subjects with prior beta-blocker plus ACE-I plus ARB use, subjects without prior beta-blocker use, subjects without prior ACE-I or ARB use, subjects with baseline LBBB, and subjects with prior hospitalisation of ≥ 180 days. However, it is noted that the sample size in these subgroups were all small, except for that of subjects with baseline LBBB, which had 888 subjects. In the subgroup of subjects with baseline LBBB, analyses of all endpoints yielded results that showed no statistically significant difference between treatment groups. The *sponsor did not provide any explanation regarding the lack of efficacy in this particular subgroup of subjects with baseline LBBB, and this will be raised as a clinical question (see Clinical Question)*. However, it is noted that analyses in the subgroup of subjects with baseline QRS > 130 msec ($n=871$) showed statistically significant relative risk reduction for eplerenone over placebo for the morbidity endpoints of all-cause hospitalisation and CV hospitalisation.

7. Clinical safety

7.1. Studies providing evaluable safety data

Only one study (A6141079) has been submitted, with 3 sets of CSRs as previously described above; amended pCSR, sCSR and OLE report. In this safety evaluation, the amended pCSR will be evaluated as the pivotal CSR.

The following study reports provided evaluable safety data:

7.1.1. Pivotal efficacy study report

The pivotal efficacy study report is the amended pCSR of Study A6141079.

In the double-blind phase of Study A6141079, the following safety data were collected:

- General adverse events (AEs) were assessed by the investigator obtaining and recording all observed or volunteered AEs, the severity (mild, moderate, or severe) of the events, and the investigator's opinion of the relationship to the study treatment.
- AEs of particular interest

There were no AEs of particular interest pre-specified in the protocol.

- Laboratory tests performed in the double-blind phase included serum potassium, creatinine, albumin, sodium, blood urea nitrogen (BUN), serum pregnancy test for women of

childbearing potential, estimated glomerular filtration rate¹⁴ (eGFR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin and haemoglobin.

- Physical examinations (including waist circumference), vital signs (blood pressure [BP] and heart rate [HR]), height, and body weight, were recorded at scheduled visits.

7.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable

7.1.3. Non-pivotal efficacy study reports

The non-pivotal efficacy study reports provided safety data, as follows:

- The sCSR provided safety data of the double-blind phase from 26 May 2010 to the end of the double-blind phase (18 March 2011; referred to in the sCSR as the “post-cut off dataset”) as well as safety data for the complete double-blind phase (30 March 2006 to 18 March 2011; referred to in the sCSR as the “complete double-blind phase dataset”). The same safety parameters were assessed as presented for the amended pCSR.
- The OLE report provided safety data of the open-label extension phase (that is, safety data from all subjects in the OLE phase from the end of their double-blind phase to the submission cut-off point date of 14 June 2011). Safety assessment in the OLE phase was based on listing of AEs, serum potassium and vital signs, which were assessed according to the schedule presented in the submission. As the OLE report consisted only of safety data without efficacy data, the study design of the OLE phase has not been previously presented in the efficacy section of this evaluation report, and will be summarised here.

In the OLE phase, all subjects who had been randomised into the double-blind phase of the trial and who had not withdrawn consent were eligible to participate in the open-label phase if their eGFR was ≥ 30 mL/min/1.73 m² at the double-blind closeout visit. Subjects with an eGFR of < 30 mL/min/1.73 m² at the double-blind closeout visit and who were confirmed to be on placebo were ineligible to participate in the open-label phase. Upon entry into the open label phase subjects will receive eplerenone 25 mg (one tablet) once daily for the first four weeks of treatment. For subjects with an eGFR of between 30-49 mL/min/1.73 m², the initial dose of eplerenone will be 25 mg (one tablet) once every other day for the first four weeks of treatment. At Week 1 of the open label phase, the dose of eplerenone would be adjusted depending on serum potassium level, according to the same protocol-specified guidelines followed by subjects in the double-blind phase. At four weeks and each subsequent clinic visit, the serum potassium level would be checked, and the eplerenone dose would be adjusted according to the same protocol-specified guidelines followed by subjects in the double-blind phase.

Overall, a total of 1155 subjects consented to participate in the OLE phase of this study. The majority was male (76.5%; 883/1155) and white (90.9%; 1050/1155). The OLE phase of the study was ongoing at the time of this TGA submission. All subjects enrolled in the open-label phase who received at least 1 dose of study drug were included in the safety analysis set.

7.1.4. Pivotal studies that assessed safety as a primary outcome

Not applicable

7.2. Patient exposure

The summary of study medication dose titration and drug exposure in the amended pCSR were presented in the submission. At Month 5, the mean dose of eplerenone was 39.5 mg and of

¹⁴ eGFR was calculated using the Modification of Diet in Renal Disease -6 (MDRD-6) formula.

placebo was 41.1 mg. At study cut off date, the mean final dose was 37.4 mg in the eplerenone group and 39.2 mg in the placebo group. The median duration of treatment from study start to study cut off was comparable between treatment groups (533.0 days and 494.0 days in the eplerenone and placebo groups, respectively).

The summary of study medication dose titration and drug exposure in the sCSR for the post-cut off dataset and for the complete double-blind phase dataset were presented in the submission. In the post-cut off dataset, at Month 5, the mean dose of eplerenone was 39.5 mg and of placebo was 40.9 mg. At the end of the double-blind phase, the mean final dose was 40.0 mg in the eplerenone group and 41.9 mg in the placebo group. The median duration of treatment in the post-cut off dataset was 141 days and 139 days in the eplerenone and placebo groups, respectively.

In the complete double-blind phase dataset, at Month 5, the mean dose of eplerenone was 39.1 mg and of placebo was 41.0 mg. At the end of the double-blind phase, the mean final dose was 37.4 mg in the eplerenone group and 39.2 mg in the placebo group. The median duration of treatment in the complete double-blind phase dataset was 675.0 days and 615.0 days in the eplerenone and placebo groups, respectively.

The extent of drug exposure and median duration of treatment in the OLE phase was not reported in the OLE report. A total of 1155 subjects were enrolled in the OLE phase. There were a total of 58 (5.0%) subjects who discontinued from the study prior to the data snapshot date of 14 June 2011.

Comments: Overall, the study drug exposure in the double-blind phase is adequate to assess if the safety profile is consistent with that reported in the Product Information.

7.3. Adverse events

7.3.1. All adverse events (irrespective of relationship to study treatment)

7.3.1.1. Pivotal study report (amended pCSR)

An overview of the number and percentage of subjects with AEs in each treatment group was presented. In the eplerenone group, 979 patients reported 3431 AEs, and in the placebo group 1007 patients reported 3530 AEs. The percentages of subjects with any AEs were 72.0% (979/1360) and 73.6% (1007/1369) in the eplerenone and placebo groups, respectively.

Treatment-emergent AEs that occurred in $\geq 2\%$ of subjects in either treatment group were presented in the submission. The most commonly reported AEs in the eplerenone group were cardiac failure (17.4% versus 21.8% in the placebo group), hyperkalemia (8.0% versus 3.7% in the placebo group), dyspnoea (4.3 % versus 5.1% in the placebo group), renal impairment (4.2% versus 2.6% in the placebo group), and dizziness (4.0% versus 4.4% in the placebo group).

7.3.1.2. Other studies

7.3.1.2.1. Supplementary CSR

An overview of the number and percentage of subjects with AEs in each treatment group for the post-cut off dataset and for the complete double-blind phase was presented. In the post-cut off dataset, 418 patients reported 890 AEs in the eplerenone group, and 406 patients reported 924 AEs in the placebo group. The percentages of subjects with any AEs were 45.3% (418/922) and 45.7% (406/889) in the eplerenone and placebo groups, respectively. In the post-cut off dataset, the most commonly reported AEs in the eplerenone group were cardiac failure (eplerenone versus placebo: 6.2% versus 5.5%), dizziness (2.6% versus 1.2%), dyspnoea (2.4 % versus 1.6%) and diabetes mellitus (2.4% versus 1.8%).

In the complete double-blind phase, 1047 patients reported 3989 AEs in the eplerenone group, and 1072 patients reported 4126 AEs in the placebo group. The percentages of subjects with any AEs were 76.8% (1047/1364) and 78.1% (1072/1372) in the eplerenone and placebo groups, respectively. In the complete double-blind phase dataset, the most commonly reported AEs in the eplerenone group were cardiac failure (eplerenone versus placebo: 20.5% versus 23.8%), hyperkalaemia (8.7% versus 4.0%), dyspnoea (5.0 % versus 5.5%), and renal impairment (5.0% versus 3.2%).

7.3.1.2.2. *OLE report*

An overview of the number and percentage of subjects with AEs in the OLE phase was presented in the sponsor's submission. A total of 246 (21.3%) subjects reported 415 AEs in the OLE phase up to the data snapshot date. The most commonly reported AEs were hyperkalemia (17 [1.5%] subjects), cardiac failure (15 [1.3%] subjects), nasopharyngitis (13 [1.1%] subjects), and chest pain (11 [1.0%] subjects).

7.3.2. **Treatment-related adverse events (adverse drug reactions)**

7.3.2.1. ***Pivotal study report (amended pCSR)***

In the eplerenone group, 280 patients reported 436 treatment-related AEs, and in the placebo group 218 patients reported 322 treatment-related AEs. The percentages of subjects with any treatment-related AEs were 20.6% (280/1360) and 15.9% (218/1369) in the eplerenone and placebo groups, respectively. Treatment-related AEs by preferred term that occurred in >1% of subjects in the eplerenone group were hyperkalaemia (6.6% versus 2.8% in the placebo group) and renal impairment (1.4% versus 0.9% in the placebo group). Out of the 90 subjects in the eplerenone group who had treatment-related AE of hyperkalaemia, 62 were of mild severity, 21 moderate and 7 severe.

7.3.2.2. ***Other studies***

7.3.2.2.1. *Supplementary CSR*

In the post-cut off dataset, 79 patients reported 93 treatment-related AEs in the eplerenone group, and 66 patients reported 79 treatment-related AEs in the placebo group. The percentages of subjects with any treatment-related AEs were 8.6% (79/922) and 7.4% (66/889) in the eplerenone and placebo groups, respectively. No treatment-related AEs occurred in $\geq 2\%$ of subjects in either treatment group. The most commonly reported treatment-related AE in the eplerenone group was hyperkalemia, reported for 9 subjects (1.0%) in the eplerenone group compared with 3 subjects (0.3%) in the placebo group. Out of the 9 subjects in the eplerenone group who had treatment-related AE of hyperkalaemia, 7 were of mild severity, 1 moderate and 1 severe.

For the complete double-blind phase, in the eplerenone group, 290 patients reported 457 treatment-related AEs, and in the placebo group 235 patients reported 348 treatment-related AEs. The percentages of subjects with any treatment-related AEs were 21.3% (290/1364) and 17.1% (235/1372) in the eplerenone and placebo groups, respectively. The only treatment-related AE that occurred in $\geq 2\%$ of subjects in either treatment group during the complete double-blind phase was hyperkalemia (7.0% and 2.9% in the eplerenone and placebo groups, respectively). Out of the 95 subjects in the eplerenone group who had treatment-related AE of hyperkalaemia, 67 were of mild severity, 21 moderate and 7 severe.

7.3.2.2.2. *OLE report*

A total of 66 (5.7%) subjects reported 82 treatment-related AEs in the OLE phase up to the data snapshot date. The most commonly reported treatment-related AE was hyperkalemia, reported by 15 [1.3%] subjects.

7.3.3. Deaths and other serious adverse events

7.3.3.1. Pivotal study report (amended pCSR)

The number of deaths reported and adjudicated was 171 (12.5%) in the eplerenone group and 213 (15.5%) in placebo group. The sponsor provided a list of the deaths but did not clearly indicate in the amended pCSR which deaths were considered related to study treatment. The incidence of each cause of death was also not clearly summarised in the amended pCSR.

Overall, 37.4% of subjects (509/1360) in the eplerenone group reported 1105 SAEs and 44.9% of subjects (614/1369) in the placebo group reported 1349 SAEs. The most frequently occurring SAE in the eplerenone group by System Organ Class (SOC) was in the SOC of cardiac disorders (22.5% versus 28.7% in the placebo group). The most frequently occurring SAEs in the eplerenone group by preferred term were cardiac failure (eplerenone versus placebo: 13.8% versus 17.8%), myocardial infarction (2.1% versus 2.1%), and death (1.9% versus 2.5%). Thirty-seven (2.7%) subjects in the eplerenone group had 50 treatment-related SAEs compared to 30 (2.2%) subjects in the placebo group who reported 38 treatment-related SAEs. A list of the most frequently reported treatment-related SAEs was not clearly summarised or listed in order in the amended pCSR. This will be raised as a clinical question (see Question 2 under Clinical Questions).

7.3.3.2. Other studies

7.3.3.2.1. Supplementary CSR

In the post-cut off dataset, 32 subjects (3.1%) in the eplerenone group and 40 subjects (4.0%) in the placebo group died. Overall, 12.0% of subjects (111/922) in the eplerenone group reported 167 SAEs and 14.4% of subjects (128/889) in the placebo group reported 213 SAEs. The only SAE reported for $\geq 2\%$ of subjects was cardiac failure (eplerenone versus placebo: 3.8% versus 3.5%). In the eplerenone group, 5 subjects (0.5%) had 5 treatment-related SAEs, compared with 1 subject (0.1%) in the placebo group with 1 treatment-related SAE.

During the complete double-blind phase, 205 subjects (15.0%) in the eplerenone group and 253 subjects (18.4%) in the placebo group died. The sponsor provided a list of the deaths but did not clearly indicate in the sCSR which deaths were considered related to study treatment. The incidence of each cause of death was also not clearly summarised in the sCSR.

For the complete double-blind phase, 43.0% of subjects (586/1364) in the eplerenone group reported 1299 SAEs and 50.0% of subjects (686/1372) in the placebo group reported 1584 SAEs. The most frequently occurring SAEs in the eplerenone group by preferred term were cardiac failure (eplerenone versus placebo: 16.0% versus 19.7%), myocardial infarction (2.1% versus 2.1%), and death (2.9% versus 3.6%). Thirty-nine (2.9%) subjects in the eplerenone group had 52 treatment-related SAEs compared to 29 (2.1%) subjects in the placebo group who reported 36 treatment-related SAEs. A list of the most frequently reported treatment-related SAEs was not clearly summarised or listed in order in the sCSR. This will be raised as a clinical question (see Question 2 under Clinical Questions below).

7.3.3.2.2. OLE report

There were a total of 22 (1.9%) deaths in the OLE phase of this study prior to the data snapshot date. A list of the deaths and causes was presented in the submission. In the OLE phase up to the data snapshot date, 82 (7.1 %) subjects reported 128 SAEs. The most frequently occurring SAE by preferred term was cardiac failure, reported by 12 (1.0%) subjects.

Sixteen (1.4%) subjects had 19 treatment-related SAEs. The most frequently occurring treatment-related SAE by preferred term were hyperkalaemia and acute renal failure, each reported by 2 (0.2%) subjects.

7.3.4. Discontinuation due to adverse events

7.3.4.1. Pivotal study report (amended pCSR)

A total of 188 (13.8%) and 222 (16.2%) of subjects in the eplerenone and placebo groups, respectively, permanently discontinued the study due to any AEs. Permanent study discontinuation due to treatment-related AEs occurred in 46 (3.4%) and 42 (3.1%) of subjects in the eplerenone and placebo groups, respectively. The sponsor has provided a listing of AEs and treatment-related AEs leading to permanent study discontinuation, but did not provide a summary of the respective incidences, and hence the most frequently reported AEs and treatment-related AEs leading to permanent study discontinuation was not reported and was not easily derived.

7.3.4.2. Other studies

7.3.4.2.1. Supplementary CSR

In the post-cut off dataset, a total of 17 (1.8%) and 30 (3.4%) of subjects in the eplerenone and placebo groups, respectively, permanently discontinued the study due to any AEs. The most commonly occurring all-causality AE leading to permanent discontinuation in the eplerenone group was cardiac failure (eplerenone versus placebo: 0.4% versus 1.0%). Permanent study discontinuation due to treatment-related AEs occurred in 3 (0.3%) and 4 (0.4%) of subjects in the eplerenone and placebo groups, respectively. The treatment-related AEs leading to permanent study discontinuation in the eplerenone group were blood creatinine increased (1 subject versus no subject in the placebo group), hyperkalaemia (1 subject versus 2 subjects in the placebo group) and renal failure (1 subject versus no subject in the placebo group).

In the complete double-blind phase dataset, a total of 215 (15.8%) and 257 (18.7%) of subjects in the eplerenone and placebo groups, respectively, discontinued the study due to any AEs. The most commonly occurring all-causality AE leading to permanent discontinuation in the eplerenone group was cardiac failure (eplerenone versus placebo: 4.3% versus 5.0%). Study discontinuation due to treatment-related AEs occurred in 52 (3.8%) and 48 (3.5%) of subjects in the eplerenone and placebo groups, respectively. The most commonly occurring treatment-related AE leading to permanent discontinuation in the eplerenone group was hyperkalemia (eplerenone versus placebo: 1.0% versus 0.8%).

7.3.4.2.2. OLE report

A total of 28 (2.4%) subjects permanently discontinued the study in the OLE phase due to AEs, with 12 (1.0%) subjects discontinuing due to treatment-related AEs. The most frequently reported AEs leading to permanent discontinuation were cardiac failure/worsening heart failure, death and hyperkalaemia, each reported by 3 subjects.

7.4. Laboratory tests

There were no significant laboratory abnormalities of concern except for serum creatinine, eGFR and serum potassium.

7.4.1. Serum Creatinine, eGFR and serum potassium

7.4.1.1. Pivotal study report (amended pCSR)

The mean serum creatinine and potassium values at each visit, and the mean change from baseline at each visit were presented in the sponsor's submission. The mean serum creatinine ranged from 0.96 to 1.55 mg/dL in the eplerenone group and 1.13 to 1.39 mg/dL in the placebo group. There were no obvious increasing trends in mean serum creatinine with time in either treatment group. The mean change from baseline in serum creatinine ranged from 0.00 to 0.33 mg/dL in the eplerenone group and 0.01 to 0.17 mg/dL in the placebo group. There were no obvious increasing trends in mean change from baseline in serum creatinine with time in either

treatment group. The mean (SD) change from baseline in serum creatinine at the final follow-up assessment was 0.09 (0.37) mg/dL in the eplerenone group and 0.04 (0.40) mg/dL in the placebo group ($p = 0.0157$).

The mean serum potassium ranged from 4.21 to 4.52 mEq/L in the eplerenone group and 4.24 to 4.41 mEq/L in the placebo group. There were no obvious increasing trends in mean serum potassium with time in either treatment group. The mean change from baseline in serum potassium ranged from -0.08 to 0.20 mEq/L in the eplerenone group and -0.08 to 0.08 mEq/L in the placebo group. There were no obvious increasing trends in mean change from baseline in serum potassium with time in either treatment group. The mean (SD) change from baseline in serum potassium at the final follow-up assessment was 0.16 (0.56) mEq/L in the eplerenone group and 0.05 (0.53) mEq/L in the placebo group ($p < 0.0001$).

The sponsor provided a summary of the incidence of hyperkalemia. The incidence of potassium levels of >5.5 mEq/L was statistically significantly higher in the eplerenone group compared to the placebo group (11.8%¹⁵ versus 7.16% $p < 0.0001$). There was no statistically significant difference in the incidence of potassium levels of >6 mEq/L between treatment groups.

The mean and median eGFR at each visit, and the mean change from baseline at each visit were presented in the submission. The mean serum eGFR ranged from 62.97 to 92.53 ml/min/1.73m² in the eplerenone group and 55.57 to 78.21 ml/min/1.73m² in the placebo group. There were no obvious decreasing trends in mean eGFR with time in either treatment group. The mean change from baseline in eGFR ranged from -11.33 to 2.83 ml/min/1.73m² in the eplerenone group and -9.8 to 3.35 mEq/L in the placebo group. There were no obvious trends in mean change from baseline in eGFR with time in either treatment group. The mean (SD) change from baseline in eGFR at the final follow-up assessment was -3.18 (18.42) ml/min/1.73m² in the eplerenone group and -1.29 (18.22) ml/min/1.73m² in the placebo group. Statistical significance was not reported in the amended pCSR.

7.4.1.2. Other studies

7.4.1.2.1. Supplementary CSR

In the post-cut off dataset, the mean serum creatinine ranged from 0.97 to 1.24 mg/dL in the eplerenone group and 1.07 to 1.67 mg/dL in the placebo group. There were no obvious increasing trends in mean serum creatinine with time in either treatment group. The mean change from baseline in serum creatinine ranged from -0.13 to 0.13 mg/dL in the eplerenone group and -0.00 to 0.17 mg/dL in the placebo group. There were no obvious increasing trends in mean change from baseline in serum creatinine with time in either treatment group. The mean (SD) change from baseline in serum creatinine at the final follow-up assessment was 0.08 (0.31) mg/dL in the eplerenone group and 0.04 (0.29) mg/dL in the placebo group ($p = 0.0034$).

In the post-cut off dataset, the mean serum potassium ranged from 4.31 to 4.55 mEq/L in the eplerenone group and 4.18 to 4.42 mEq/L in the placebo group. There were no obvious increasing trends in mean serum potassium with time in either treatment group. The mean change from baseline in serum potassium ranged from 0.01 to 0.23 mEq/L in the eplerenone group and -0.14 to 0.08 mEq/L in the placebo group. There were no obvious increasing trends in mean change from baseline in serum potassium with time in either treatment group. The mean (SD) change from baseline in serum potassium at the final follow-up assessment was 0.18 (0.53) mEq/L in the eplerenone group and 0.05 (0.48) mEq/L in the placebo group ($p < 0.0001$).

The sponsor provided a summary of the incidence of hyperkalemia in the post-cut off dataset. In the post-cut off dataset, there were no statistically significant differences between treatment groups in the incidences of potassium levels of >5.5 mEq/L and of > 6 mEq/L.

¹⁵ Sponsor comment: 11.83%

In the post-cut off dataset, the mean serum eGFR ranged from 67.01 to 81.19 ml/min/1.73m² in the eplerenone group and 42.80 to 74.75 ml/min/1.73m² in the placebo group. There were no obvious decreasing trends in mean eGFR with time in either treatment group. The mean (SD) change from baseline in eGFR at the final follow-up assessment was -3.96 (19.63) ml/min/1.73m² in the eplerenone group and -1.73 (19.49) ml/min/1.73m² in the placebo group. Statistical significance was not reported.

In the complete double-blind phase, the mean serum creatinine ranged from 0.96 to 1.36 mg/dL in the eplerenone group and 1.08 to 1.35 mg/dL in the placebo group. There were no obvious increasing trends in mean serum creatinine with time in either treatment group. The mean change from baseline in serum creatinine ranged from -0.04 to 0.22 mg/dL in the eplerenone group and 0.01 to 0.10 mg/dL in the placebo group. There were no obvious increasing trends in mean change from baseline in serum creatinine with time in either treatment group. The mean (SD) change from baseline in serum creatinine at the final follow-up assessment was 0.10 (0.37) mg/dL in the eplerenone group and 0.06 (0.40) mg/dL in the placebo group (p = 0.0045).

In the complete double-blind phase, the mean serum potassium ranged from 4.32 to 4.53 mEq/L in the eplerenone group and 4.32 to 4.40 mEq/L in the placebo group. There were no obvious increasing trends in mean serum potassium with time in either treatment group. The mean change from baseline in serum potassium ranged from 0.13 to 0.24 mEq/L in the eplerenone group and 0.01 to 0.09 mEq/L in the placebo group. There were no obvious increasing trends in mean change from baseline in serum potassium with time in either treatment group. The mean (SD) change from baseline in serum potassium at the final follow-up assessment was 0.16 (0.57) mEq/L in the eplerenone group and 0.05 (0.54) mEq/L in the placebo group (p <0.0001).

The sponsor provided a summary of the incidence of hyperkalemia. In the complete double-blind phase, the incidence of potassium levels of >5.5 mEq/L was statistically significantly higher in the eplerenone group compared to the placebo group (12.87% versus 8.23%, p <0.0001). There was no statistically significant difference between treatment groups in the incidence of potassium levels of > 6 mEq/L.

In the complete double-blind phase, the mean serum eGFR ranged from 64.35 to 92.53 ml/min/1.73m² in the eplerenone group and 55.57 to 72.06 ml/min/1.73m² in the placebo group. There were no obvious increasing trends in mean eGFR with time in either treatment group. The mean (SD) change from baseline in eGFR at the final follow-up assessment was -3.94 (19.58) ml/min/1.73m² in the eplerenone group and -1.81 (18.97) ml/min/1.73m² in the placebo group. Statistical significance was not reported.

7.4.1.2.2. OLE report

Serum creatinine and eGFR were not assessed in the OLE phase. Analyses of serum potassium in the subjects in the OLE phase showed that 7.46% (82/1099) of subjects and 5.19% (57/1099) of subjects had serum potassium > 5.5 mEq/L and >6 mEq/L, respectively.

7.5. Vital signs

7.5.1. Pivotal study report (amended pCSR)

There were statistically significantly greater mean reductions from baseline in the systolic blood pressure (SBP) and in the diastolic blood pressure (DBP) in the eplerenone group compared to the placebo group. At the final follow-up assessment, the mean change from baseline in SBP was -2.47 mm Hg in the eplerenone group and -0.25 mm Hg in the placebo group. This difference was found to be statistically significant (p = 0.0005). The mean change from baseline in DBP at the final follow-up assessment was -1.83 mm Hg in the eplerenone group and -0.71 mm Hg in the placebo group. This difference was also found to be statistically significant (p = 0.0014). The median changes from baseline to last observation in SBP was -2.00mmHg and 0.00mmHg in the

eplerenone and placebo group, respectively, and that in DBP were 0.00 mmHg in both treatment groups.

7.5.2. Other studies

7.5.2.1. Supplementary CSR

In the post-cut off dataset, there were statistically significant differences between treatment groups in the mean change from baseline in both SBP and DBP at the final follow-up assessment (eplerenone versus placebo: -2.38 versus -0.37 mm Hg, $p = 0.0059$ for SBP; -2.19 versus -0.79 mm Hg, $p = 0.0014$ for DBP).

In the complete double-blind phase data, there were also statistically significant differences between treatment groups in the mean change from baseline in both SBP and DBP at the final follow-up assessment (-2.78 versus -1.33 mm Hg, $p=0.0263$ for SBP; -2.06 versus -1.09 mm Hg, $p= 0.0039$ for DBP).

7.5.2.2. OLE report

The mean (SD) changes from baseline to last observation in SBP and DBP were -1.53 (15.96) mmHg and -1.21 (11.66) mmHg, respectively.

7.6. Postmarketing experience

No detailed postmarketing data was provided. The sponsor has stated that in support of this submission, Pfizer's postmarketing safety database was searched cumulatively for all medically confirmed, nonclinical study eplerenone cases reported through 31 January 2011. This was briefly summarised in the sponsor's Clinical Overview. It showed that the most frequently reported AE was hyperkalaemia, and that the overall postmarketing analyses were consistent with the known safety profile of eplerenone.

The proposed Product Information (PI) contains data regarding postmarketing experience which is unamended from the currently-approved PI, and states that

"In post-marketing experience, the following additional undesirable effects have been reported: Skin and subcutaneous tissues disorders Angioneurotic oedema, rash".

7.7. Other safety issues

7.7.1. Safety in special populations

As previously described, the sponsor has stated that in order to fulfil a European post-approval commitment issued at the time of approval on 10 March 2004, efficacy and safety analyses were also conducted during the double-blind phase of Study A6141079 for the "very elderly" subjects in the study, defined as subjects aged ≥ 75 years.

7.7.1.1. Pivotal study report (amended pCSR)

An overview of the number and percentage of subjects of age ≥ 75 years with AEs in each treatment group was submitted. The percentages of subjects of age ≥ 75 years with any AEs were 78.2% (258/330) and 76.5% (250/327) in the eplerenone and placebo groups, respectively. In the subgroup of subjects of age < 75 years the incidence of any AEs were 70.0% (721/1030) and 72.6% (757/1042) in the eplerenone and placebo groups, respectively. The most commonly reported AEs in the eplerenone group in this subgroup¹⁶ were cardiac failure (eplerenone versus placebo: 22.7% versus 29.4%), hyperkalemia (9.4% versus 3.7%), renal

¹⁶ Sponsor comment: Age ≥ 75 years.

impairment (6.1% versus 3.4%), bronchitis (5.2 % versus 6.7%), hypotension (4.8% versus 3.4%), atrial fibrillation (4.5% versus 4.3%) and back pain (4.2% versus 2.4%).

An overview of the number and percentage of subjects of age ≥ 75 years with treatment-related AEs in each treatment group was submitted. The percentages of subjects of age ≥ 75 years with any treatment-related AEs were 26.7% (88/330) and 17.4% (57/327) in the eplerenone and placebo groups, respectively. In the subgroup of subjects of age < 75 years the incidence of any treatment-related AEs were 18.6% (192/1030) and 15.5% (161/1042) in the eplerenone and placebo groups, respectively. The most commonly reported AEs treatment-related AEs by preferred term in the eplerenone group in this subgroup¹⁷ were hyperkalaemia (eplerenone versus placebo: 7.6% versus 2.8%), renal impairment (2.4% versus 1.5%), and blood creatinine increased (2.1% versus 0.9%). Out of the 25 subjects of age ≥ 75 years in the eplerenone group who had treatment-related AE of hyperkalaemia, 18 were of mild severity, 6 moderate and 1 severe.

The percentages of subjects of age ≥ 75 years with any SAEs were 42.7 % (141/330) and 52.9% (173/327) in the eplerenone and placebo groups, respectively. In the subgroup of subjects of age < 75 years the incidence of any SAEs were 35.7% (368/1030) and 42.3% (441/1042), respectively. The most frequently occurring SAE in subjects of age ≥ 75 years in the eplerenone group by SOC was cardiac disorders (eplerenone versus placebo: 20.9% versus 26.4%). The most frequently occurring SAEs in subjects of age ≥ 75 years in the eplerenone group by preferred term were cardiac failure (16.7% versus 23.2%), myocardial infarction (3.0% versus 3.4%) and renal impairment (3.0% versus 1.8%).

Fourteen (4.2%) subjects of age ≥ 75 years in the eplerenone group had 20 treatment-related SAEs compared to 9 (2.8%) subjects of age ≥ 75 years in the placebo group who reported 11 treatment-related SAEs. A list of the most frequently reported treatment-related SAEs was not clearly summarised in order of frequency in the main content of the amended pCSR, but a look through the listing of treatment-related SAEs in subjects of age ≥ 75 years showed that the most frequently reported treatment-related SAEs in the eplerenone group in this subgroup were hyperkalaemia (eplerenone versus placebo: 1.2% versus 0.6%) and renal impairment (0.9% versus 0.6%).

The incidences of deaths in the subgroup of subjects aged ≥ 75 years and aged < 75 years were not summarised by the sponsor in the main content of the amended pCSR, but a look through the listing of all-causality AEs in the subgroup of subjects aged ≥ 75 years showed that there were 9 (2.7%) AEs under the preferred term of "death" in the eplerenone group and 6 (1.8%) in the placebo group. In this subgroup, there were no incidences of "death" in either treatment group in the listing of study treatment-related AEs. A look through the listing of all-causality AEs in the subgroup of subjects aged < 75 years showed that there were 17 (1.7%) AEs under the preferred term of "death" in the eplerenone group, and 29 (2.8%) in the placebo group. In the listing of study treatment-related AEs in this subgroup, there were no incidences of "death" in the eplerenone treatment group and 2 deaths (0.2%) in the placebo group.

In subjects of age ≥ 75 years, the mean serum creatinine ranged from 0.93 to 1.69 mg/dL in the eplerenone group and 1.03 to 1.86 mg/dL in the placebo group. There were no obvious increasing trends in mean serum creatinine with time in either treatment group. The mean change from baseline in serum creatinine ranged from -0.15 to 0.35 mg/dL in the eplerenone group and -0.65 to 0.50 mg/dL in the placebo group. There were no obvious increasing trends in mean change from baseline in serum creatinine with time in either treatment group. The mean (SD) change from baseline in serum creatinine at the final follow-up assessment was 0.12 (0.36) mg/dL in the eplerenone group and 0.08 (0.38) mg/dL in the placebo group ($p = 0.2502$).

¹⁷ Sponsor comment: Age \geq 75 years.

In subjects of age ≥ 75 years, the mean serum potassium ranged from 3.94 to 4.55 mEq/L in the eplerenone group and 4.29 to 4.48 mEq/L in the placebo group. There were no obvious increasing trends in mean serum potassium with time in either treatment group. The mean change from baseline in serum potassium ranged from 0.15 to 0.25 mEq/L in the eplerenone group and -0.10 to 0.19 mEq/L in the placebo group. There were no obvious increasing trends in mean change from baseline in serum potassium with time in either treatment group. The mean (SD) change from baseline in serum potassium at the final follow-up assessment was 0.18 (0.57) mEq/L in the eplerenone group and 0.04 (0.57) mEq/L in the placebo group ($p < 0.0001$).

The sponsor has provided a summary of the incidence of hyperkalemia in subjects of age ≥ 75 years and < 75 years. The incidence of potassium levels of >5.5 mEq/L was statistically significantly higher in the eplerenone group compared to the placebo group in both age group categories. In subjects of age ≥ 75 years the incidences of potassium levels of >5.5 mEq/L were 12.42% and 6.60% in the eplerenone and placebo groups, respectively ($p < 0.0001$). In subjects of age < 75 years the incidences of potassium levels of >5.5 mEq/L were 11.64% and 7.34% in the eplerenone and placebo groups, respectively ($p = 0.0011$). There was no statistically significant difference in the incidence of potassium levels of >6 mEq/L between treatment groups in both age group categories.

In subjects of age ≥ 75 years, the mean serum eGFR ranged from 47.48 to 70.90 ml/min/1.73m² in the eplerenone group and 44.20 to 68.34 ml/min/1.73m² in the placebo group. There were no obvious decreasing trends in mean eGFR with time in either treatment group. The mean change from baseline in eGFR ranged from -14.53 to 12.00 ml/min/1.73m² in the eplerenone group and -9.80 to 4.22 mEq/L in the placebo group. There were no obvious trends in mean change from baseline in eGFR with time in either treatment group. The mean (SD) change from baseline in eGFR at the final follow-up assessment was -5.29 (17.56) ml/min/1.73m² in the eplerenone group and -4.07 (15.38) ml/min/1.73m² in the placebo group. Statistical significance was not reported.

In subjects ≥ 75 years of age, there was a statistically significant difference between the treatment groups in mean change from baseline in SBP at the final follow-up assessment (-4.75 mm Hg in the eplerenone group and -0.70 mm Hg in the placebo group [$p = 0.0315$]). There were no statistically significant differences between treatment groups in the mean change from baseline at the final follow-up assessment for DBP, pulse pressure, or pulse rate, in subjects ≥ 75 years of age. The median changes from baseline to last observation in SBP was -5.00mmHg and 0.00mmHg in the eplerenone and placebo groups, respectively, and that in DBP were -3.00 mmHg and 0.00mmHg, respectively. In subjects < 75 years of age, there was a statistically significant difference between the treatment groups in mean change from baseline in SBP at the final follow-up assessment (-1.75 mm Hg in the eplerenone group and -0.11 mm Hg in the placebo group [$p = 0.0058$]), as well as for DBP (-1.40 mm Hg in the eplerenone group and -0.54 mm Hg in the placebo group [$p = 0.0101$]). In this subgroup, the median changes from baseline to last observation in SBP and DBP were 0.00mmHg in both treatment groups.

7.7.1.2. Other studies

7.7.1.2.1. Supplementary CSR

An overview of the number and percentage of subjects of age ≥ 75 years with AEs in each treatment group in the post-cut off dataset and in the complete double-blind phase dataset was submitted.

In the post-cut off dataset, the percentages of subjects of age ≥ 75 years with any AEs were 52.7% (106/201) and 50.5% (100/198) in the eplerenone and placebo groups, respectively. In the subgroup of subjects of age < 75 years the incidence of any AEs were 43.4% (312/721) and 44.3% (306/691) in the eplerenone and placebo groups, respectively. The most commonly reported AEs in the eplerenone group in subjects of age ≥ 75 years in the post-cut off dataset were cardiac failure (8.0% versus 10.1% in the placebo group), and dizziness (4.5% versus

2.0% in the placebo group). The incidence of hyperkalaemia reported as AE in subjects of age \geq 75 years in the post-cut off dataset was 1.5% and 1.0% in the eplerenone and placebo groups, respectively.

For the post-cut off dataset, the percentages of subjects of age \geq 75 years with any treatment-related AEs were 13.4% (27/201) and 10.6% (21/198) in the eplerenone and placebo groups, respectively. In the subgroup of subjects of age $<$ 75 years the incidence of any treatment-related AEs were 7.2% (52/721) and 6.5% (45/691) in the eplerenone and placebo groups, respectively. No treatment-related AEs occurred in $>$ 2% of subjects of age \geq 75 years in any treatment group in the post-cut off dataset. The most commonly reported treatment-related AEs in the eplerenone group in this subgroup were dizziness, fatigue, and blood creatinine increased, each with an incidence of 1.5% versus 0.5% in the placebo group.

For the post-cut off dataset, the percentages of subjects of age \geq 75 years with any SAEs were 17.4 % (35/201) and 20.2% (40/198) in the eplerenone and placebo groups, respectively. In the subgroup of subjects of age $<$ 75 years the incidence of any SAEs were 10.5% (76/721) and 12.7% (88/691) in the eplerenone and placebo groups, respectively. The most frequently occurring SAE in subjects of age \geq 75 years in the eplerenone group was cardiac failure (4.0% versus 5.6% in the placebo group). In the post-cut off dataset, $<$ 1% of subjects in either age subgroup (\geq 75 years old or $<$ 75 years old) experienced treatment-related SAEs in either treatment group.

A summary of the incidence of hyperkalemia in subjects of age \geq 75 years and $<$ 75 years in the post-cut off dataset was submitted. For the post-cut off dataset, there was no statistically significant difference in the incidence of potassium levels of $>$ 5.5 mEq/L and of $>$ 6 mEq/L between treatment groups in subjects of age \geq 75 years and in subjects of age $<$ 75 years.

In the complete double-blind phase dataset, the percentages of subjects of age \geq 75 years with any AEs were 82.4% (272/330) and 82.6% (271/328) in the eplerenone and placebo groups, respectively. In the subgroup of subjects of age $<$ 75 years, the incidence of any AEs were 75.0% (775/1034) and 76.7% (801/1044) in the eplerenone and placebo groups, respectively. The most commonly reported AEs in the eplerenone group in subjects of age \geq 75 years in the complete double-blind phase dataset were cardiac failure (eplerenone versus placebo: 27.0% versus 32.3%), hyperkalaemia (10.3% versus 4.3%), and renal impairment (6.4% versus 4.0%).

In the complete double-blind phase dataset, the percentages of subjects of age \geq 75 years with any treatment-related AEs were 28.5% (94/330) and 19.2% (63/328) in the eplerenone and placebo groups, respectively. In the subgroup of subjects of age $<$ 75 years the incidence of any treatment-related AEs were 19.0% (196/1034) and 16.5% (172/1044) in the eplerenone and placebo groups, respectively. The most commonly reported treatment-related AEs in the eplerenone group in subjects of age \geq 75 years in the complete double-blind phase dataset were hyperkalaemia (eplerenone versus placebo: 8.5% versus 3.0%), renal impairment (2.4% versus 1.5%), increased blood creatinine (2.4% versus 0.9%), and hypotension (2.4% versus 0.3%).

In the complete double-blind phase dataset, the percentages of subjects of age \geq 75 years with any SAEs were 47.9 % (158/330) and 58.8% (193/328) in the eplerenone and placebo groups, respectively. In the subgroup of subjects of age $<$ 75 years the incidence of any SAEs were 41.4% (428/1034) and 47.2% (493/1044) in the eplerenone and placebo groups, respectively. The most frequently occurring SAE in subjects of age \geq 75 years in the eplerenone group was cardiac failure (eplerenone versus placebo: 18.8% versus 25.9%). For the complete double-blind phase, among subjects \geq 75 years of age, 4.2% of subjects in the eplerenone group and 2.7% of subjects in the placebo group experienced treatment-related SAEs. Among subjects $<$ 75 years of age, 2.4% of subjects in the eplerenone group and 1.9% of subjects in the placebo group experienced SAEs considered treatment related. The most frequently occurring treatment-related SAE in subjects of age \geq 75 years in the eplerenone group were hyperkalaemia (1.2 % versus 0.6%) and renal impairment (0.9% versus 0.6%).

A summary of the incidence of hyperkalemia in subjects of age ≥ 75 years and < 75 years in the complete double-blind phase dataset was submitted. In the complete double-blind phase dataset, the incidence of potassium levels of >5.5 mEq/L was statistically significantly higher in the eplerenone than placebo group in subjects of age ≥ 75 years (13.93% and 7.52% in the eplerenone and placebo groups, respectively; $p=0.0105$), and in subjects of age < 75 years (12.54% and 8.45% in the eplerenone and placebo groups, respectively ($p=0.0031$)). There was no statistically significant difference in the incidence of potassium levels of > 6 mEq/L between treatment groups in subjects of age ≥ 75 years and in subjects of age < 75 years.

7.7.1.2.2. OLE report

Analysis on the subgroup of subjects' ≥ 75 years old was not done for the OLE phase.

7.8. Evaluator's overall conclusions on clinical safety

Overall, the incidence of all-causality AEs and all-causality SAEs was comparable between the 2 treatment groups. However, the incidences of treatment-related AEs and treatment-related SAEs were higher in the eplerenone group than in the placebo group (20.6% versus 15.9%, and 2.7% versus 2.2%, respectively).

The safety results of the study were consistent with the known adverse effects of eplerenone. The AEs elicited in this study are known adverse effects of eplerenone stated in the currently-approved Australian PI for eplerenone. Safety results in the complete double-blind phase dataset and in the OLE phase were consistent with those of the double-blind phase up to 25 May 2010.

The most commonly occurring treatment-related AE in the eplerenone group was hyperkalaemia, which is a known adverse effect of eplerenone stated in the currently-approved Australian PI. The incidence of hyperkalaemia reported as treatment-related AE with administration of eplerenone was 8.0% (compared with 3.7% in the placebo group) in the double-blind phase up to 25 May 2010, and 8.7% (compared with 4.0% in the placebo group) in the complete double-blind phase. This incidence is higher compared to that in the EPHEBUS study, the registration study for eplerenone, where the incidence of hyperkalaemia with administration of eplerenone was 3.4% (compared with 2.0% in the placebo group)¹⁸. However, the study population in EPHEBUS was different from that of Study A6141079, and involved patients randomised 3 to 14 days after an acute myocardial infarction, and who were on different concomitant medications compared to the study patients in Study A6141079. It is noted that in Study A6141079, the majority of hyperkalaemia which were reported as treatment-related AEs were mild in severity¹⁹. It is also noted by the evaluator that in the new proposed PI, the sponsor has added the precaution of increased risk of hyperkalaemia when eplerenone is used in combination with ACE-Is or ARBs. In addition, although the incidence of serum potassium > 5.5 mEq/L was statistically significantly higher in the eplerenone group compared to placebo group, there was no statistically significant difference between treatment groups in the incidence of serum potassium > 6 mEq/L. Efficacy results in the double-blind phase up to 25 May 2010 had also shown that there were no statistically significant difference in the occurrence of hospitalisation for hyperkalaemia between eplerenone group and placebo group.

The observed increase in serum creatinine with eplerenone is also a known adverse effect of eplerenone listed in the currently-approved PI as "*renal function abnormal*". It is noted that the

¹⁸ Currently approved PI in Australia for eplerenone

¹⁹ In the double-blind phase up to 25 May 2010, out of the 90 subjects in the eplerenone group who had treatment-related AE of hyperkalaemia, 62 were of mild severity, 21 moderate and 7 severe. In the complete double-blind phase, out of the 95 subjects in the eplerenone group who had treatment-related AE of hyperkalaemia, 67 were of mild severity, 21 moderate and 7 severe.

mean change from baseline in serum creatinine at the final follow-up assessment in the eplerenone group, although statistically significantly more compared to the placebo group, was small (about 0.1 mg/dL). The associated mean decrease from baseline in eGFR at the final follow-up assessment in the eplerenone group was also small (up to about -4 ml/min/1.73m²). There were also no obvious trends in mean change from baseline in serum creatinine or eGFR with time in the eplerenone group. Efficacy results in the double-blind phase up to 25 May 2010 had also shown that there was no statistically significant difference in the occurrence of hospitalisation for worsening renal function between eplerenone group and placebo group.

The observed drop in SBP and DBP with eplerenone is a known adverse effect of eplerenone listed in the currently-approved PI as “hypotension”. Although the mean changes from baseline in SBP and DBP at final follow-up assessment in the eplerenone group were small (mean change from baseline of up to -2.8mmHg in SBP and -2.2mmHg in DBP), the sponsor did not provide an analysis of the responder rates in terms of the degree of reduction in SBP and DBP, which would allow better evaluation of the hypotensive effect of eplerenone on the study population. (see Question 4 under *Clinical Questions* below). The incidence of death in the safety analysis supported the efficacy results that there was no increased risk of overall mortality compared to placebo. However, although the sponsor provided a list of deaths for all 3 sets of CSRs, it was not clearly summarised or indicated as to which deaths were considered related to study treatment, and the incidence of each cause of death was not summarised. As a result the incidence of treatment-related deaths and of each cause of death could not be compared between the eplerenone and placebo groups. This will be raised as a clinical question (see Question 1 under *Clinical Questions* below).

Overall safety analyses results in the subgroup of patients aged ≥ 75 years were consistent with those in the overall study population. Safety analyses in the subgroup of patients aged ≥ 75 years showed that the incidences of all-causality AEs, treatment-related AEs, all-causality SAEs, and treatment-related SAEs were higher in this subgroup of patients in the eplerenone group compared to those in the overall study population and to those aged < 75 years. However the incidences of these AEs and SAEs were also higher in the placebo group in the subgroup of patients aged ≥ 75 years compared with the respective placebo groups in the overall study population and in the subgroup of patients aged < 75 years. This suggests that the higher incidences of these AEs and SAEs seen in the eplerenone groups in the subgroup of patients aged ≥ 75 years might be reflecting the generally higher incidence of AEs or SAEs in the more elderly age group, rather than an actual adverse effect of eplerenone on the subgroup of elderly patients.

The profile of the most commonly reported AEs and SAEs in the eplerenone group in this subgroup of patients aged ≥ 75 years is comparable with that in the overall study population and that in the subgroup of patients aged < 75 years. The mean changes from baseline in serum potassium, serum creatinine and eGFR at the final follow-up assessment in the eplerenone group were also comparable between the subgroup of patients aged ≥ 75 years and in the overall study population. In addition, the incidence of serum potassium levels of >5.5 mEq/L in the eplerenone group in the subgroup of patients aged ≥ 75 years (12.42%) was similar to that in the overall study population (11.80%) and that in the subgroup of patients aged < 75 years (11.64%). Consistent with the results in the overall population, there was no statistically significant difference between treatment groups in the incidence of potassium levels of >6 mEq/L in this subgroup of patients aged ≥ 75 years.

The mean change from baseline in SBP at final follow-up assessment in the eplerenone group in the subgroup of patients aged ≥ 75 years (-4.75mmHg) was greater compared to the overall study population (-2.47 mmHg) and in the subgroup of patients aged < 75 years (-1.75mmHg). Although the mean change from baseline in DBP at final follow-up assessment in the subgroup of patients aged ≥ 75 years was not statistically significantly different between treatment groups, it was also greater in this subgroup of patients aged ≥ 75 years (-3.19mmHg) compared

to the overall study population (-1.83 mmHg) and in the subgroup of patients aged < 75 years (-1.40 mmHg). The sponsor did not provide an analysis of the responder rates in terms of the degree of reduction in SBP and DBP in this subgroup of patients, which would allow better evaluation of the hypotensive effect of eplerenone on this elderly study population (see Question 4 under *Clinical Questions* below).

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of eplerenone in the proposed usage are:

- Potential reduction in the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II chronic heart failure when used in addition to standard heart failure therapy

According to statistics gathered by the Australian Institute of Health and Welfare (AIHW) and the National Heart Foundation of Australia (NHFA)²⁰, at least 300 000 Australians had chronic heart failure, with 30,000 new cases diagnosed each year. Heart failure accounted for 9.5% of hospitalisations for heart, stroke and vascular diseases, and was the third largest cause of death from heart, stroke and vascular diseases in Australia. There is thus potential benefit in the availability of a drug that can reduce mortality or morbidity arising from chronic heart failure.

The TGA-adopted EMA guidelines on the clinical investigation of drugs for treatment of cardiac failure³ recommend that the preferred primary endpoint of heart failure treatment studies be all-cause mortality, but that “*provided that a deleterious effect on mortality is ruled out, improvement in symptoms and correlation of haemodynamic improvement with clinical findings can be accepted as evidence of efficacy*”. This is based on the principle that the main objective is to demonstrate improvement in cardiovascular morbidity and clinical symptoms, and no adverse effect on overall mortality. Overall, the efficacy results of Study A6141079 had managed to demonstrate improvement in cardiovascular morbidity and no adverse effect on overall mortality.

Efficacy analysis results showed that there was a statistically significant 37% relative risk reduction in the incidence of the primary composite endpoint of CV mortality or hospitalisation for HF in the eplerenone group compared to the placebo group. There was statistically significant relative risk reduction of 23.9% in all-cause mortality for eplerenone compared to placebo, as well as statistically significant relative risk reductions of 42% in hospitalisation for HF and of 31% in CV hospitalisation for eplerenone compared to placebo.

Subgroup analyses²¹ of the mortality endpoints of all-cause death and CV death showed that there was no statistically significant greater risk of all-cause or CV mortality in the eplerenone group compared to placebo across the subgroups. Subgroup analyses¹³ of the morbidity endpoints were difficult to interpret in certain subgroups with small sample sizes, but in general showed that there was no obvious indication that eplerenone was less effective in certain subgroups across the endpoints, except for the subgroup of subjects with baseline LBBB, where analyses of all efficacy endpoints yielded results that showed no statistically significant difference between treatment groups. This needs to be evaluated in the context of the safety profile for this subgroup of patients (see Question 3 under *Clinical Questions* below).

²⁰ Australian Institute of Health and Welfare (AIHW) and the National Heart Foundation of Australia (NHFA). Heart, stroke and vascular diseases—Australian facts 2004.

²¹ Including for the subgroup of patients of age ≥ 75 years.

8.2. First round assessment of risks

The risks of eplerenone in the proposed indication are:

- hyperkalaemia,
- increase in serum creatinine and associated decrease in eGFR
- drop in systolic and diastolic blood pressure

The safety results of the study were consistent with the known adverse effects of eplerenone stated in the currently-approved Australian PI. The potential risks of eplerenone listed above were all known adverse effects of eplerenone.

The most commonly occurring treatment-related AE in the eplerenone group in this study was hyperkalaemia. However, the majority of AEs of hyperkalaemia which were reported as treatment-related AEs were mild in severity. In addition, although the incidences of serum potassium > 5.5 mEq/L was statistically significantly higher in the eplerenone group compared to placebo group, there was no statistically significant difference between treatment groups in the incidence of serum potassium > 6 mEq/L. It also needs to be taken into consideration that this adverse effect of eplerenone can be monitored by routine laboratory assessment.

With regards to changes in serum creatinine and eGFR, the mean changes from baseline in serum creatinine and of eGFR at the final follow-up assessment in the eplerenone group were small and not clinically significant. There were also no obvious trends in mean change from baseline in serum creatinine or eGFR with time in the eplerenone group. It is also noted that these adverse effects of eplerenone can also be monitored by routine laboratory assessment.

Although decreases in systolic and diastolic blood pressure were statistically significantly more in the eplerenone group compared to the placebo group, this is a known adverse effect of eplerenone, and is an adverse effect that can be assessed with non-invasive blood pressure monitoring. In addition, it is noted that the incidence of hypotension reported as treatment-related AE in the overall study population in the pivotal CSR (that is, amended pCSR) was low (eplerenone versus placebo: 1.1% versus 0.3%).

Overall safety analyses results in the subgroup of patients aged ≥ 75 years were consistent with those in the overall study population, and did not indicate significantly greater safety concerns in this age group with the use of eplerenone. Although the incidences of all-causality AEs, treatment-related AEs, all-causality SAEs and treatment-related SAEs were higher in this subgroup of patients in the eplerenone group compared to those in the overall study population and to those aged < 75 years, the incidences were also higher in the placebo group in the subgroup of patients aged ≥ 75 years compared with the respective placebo groups in the overall study population and in the subgroup of patients aged < 75 years. This suggests that the higher incidences of these AEs and SAEs seen in the eplerenone groups in the subgroup of patients aged ≥ 75 years might be reflecting the generally higher incidence of AEs or SAEs in this more elderly age group, rather than an actual adverse effect of eplerenone in the subgroup of elderly patients. The profile of the most commonly reported AEs and SAEs, mean changes from baseline in serum potassium, serum creatinine and eGFR at the final follow-up assessment, and incidence of serum potassium levels of >5.5 mEq/L in the eplerenone group in this subgroup of patients aged ≥ 75 years were all comparable with that in the overall study population and that in the subgroup of patients aged < 75 years.

However, the mean change from baseline in SBP and DBP at final follow-up assessment in the eplerenone group in the subgroup of patients aged ≥ 75 years was greater compared to the overall study population and to the subgroup of patients aged < 75 years. Although it is noted that the incidence of hypotension reported as treatment-related AE in the subgroup of patients aged ≥ 75 years in the pivotal CSR (that is, amended pCSR) was low (eplerenone versus placebo; ≥ 75 years old: 0.9% versus 0.3%; < 75 years old: 1.8% versus 0.3%), further analysis

comparing the responder rates in terms of reductions in SBP and DBP in age-stratified groups, is needed to fully evaluate if eplerenone has a greater risk of hypotension in the elderly patient population (see Question 4 under *Clinical Questions* below). First round assessment of benefit-risk balance

The benefit-risk balance of eplerenone given the proposed usage was favourable.

Efficacy results of Study A6141079 demonstrated improvement in cardiovascular morbidity and no adverse effect on overall mortality. Efficacy results showed a statistically significant relative risk reduction of 23.9% in all-cause mortality for eplerenone compared to placebo, as well as statistically significant relative risk reductions of 42% in hospitalisation for HF and of 31% in CV hospitalisation for eplerenone compared to placebo.

The safety results of the study were consistent with the known adverse effects of eplerenone stated in the currently-approved Australian PI. The potential risks of eplerenone elicited in Study A6141079 were hyperkalaemia, increase in serum creatinine and associated decrease in eGFR, and drop in systolic and diastolic blood pressure, which were all known adverse effects of eplerenone, and could be monitored by routine laboratory assessment or non-invasive blood pressure monitoring.

8.3. First round recommendation regarding authorisation

It is recommended that the application for extension of indication of eplerenone for treatment of adult patients with NYHA class II chronic heart failure, as an addition to standard optimal therapy, be approved.

This is subject to a satisfactory response to the recommended changes in the PI and CMI and to the clinical questions raised (see *Clinical Questions* below). In addition it was noted that the sponsor has stated that the OLE report provided in this submission was a snapshot of the safety data from the OLE phase up to the 14 June 2011 data snapshot, and that in order to present the most current interim safety update for this submission, data cleaning was still ongoing while a database snapshot was made on 14 June 2011 and the database was not fully reconciled at the time of the data snapshot. It is recommended that the sponsor provide to the TGA the final OLE CSR based on a complete and validated OLE database as soon as this becomes available.

9. Clinical questions

9.1. Efficacy

1. Please provide the rationale for the inclusion criterion of $eGFR \geq 30 \text{ mL/min/1.73 m}^2$ in study A6141079 (*Emphasis-HF Study*).

Rationale for question above:

As commented above, the currently-approved Australian PI for eplerenone stated that "INSPIRA should not be administered to patients with moderate to severe renal insufficiency (creatinine clearance $<50 \text{ mL/min}$)". No clear rationale was given by the sponsor as to why patients with $eGFR \geq 30 \text{ mL/min/1.73 m}^2$ were included in the Emphasis-HF study.

It is noted by the evaluator that in the sponsor's Clinical Overview of this submission, the sponsor has stated that "*This is the first large study with an aldosterone antagonist that included subjects with moderate renal impairment ($eGFR 30$ to $49 \text{ mL/min/1.73 m}^2$). Unlike in the EPHEBUS trial where patients were excluded with moderate renal impairment, the present study enrolled subjects with mild and moderate renal impairment.*" It appeared to the evaluator that the sponsor had meant that the inclusion of subjects with $eGFR$ of 30 to $49 \text{ mL/min/1.73 m}^2$ was planned prospectively with the intention of evaluating the efficacy and safety in this group of

patients. However, this was not clearly stated in the study protocol or study report, and was not included in the objective of the study.

2. Please justify the dosing regimen for subjects with eGFR between 30 to 49 mL/min/1.73 m² of 25mg eplerenone every other day.

Rationale for question above:

As commented above, in the study, the starting dose of eplerenone and the subsequent titration schedule according to serum potassium levels for subjects with eGFR ≥ 50 mL/min/1.73 m² were consistent with the dosing recommendation in the currently-approved Australian PI for eplerenone. However, the rationale for the dosing regimen for subjects with eGFR between 30 to 49 mL/min/1.73 m² was not given in the CSRs. The references to dosing in patients with renal impairment in the currently-approved PI are restricted to that “*INSPIRA should not be administered to patients with moderate to severe renal insufficiency (creatinine clearance <50mL/min)*”, that “*No initial dose adjustment is required in patients with mild renal impairment*” and that “*INSPIRA is contraindicated in patients with severe renal insufficiency*”.

3. Please provide information for the pivotal study report (i.e. amended pCSR) on the number of subjects in each treatment group with each category of protocol deviations.

Rationale for question above:

As commented above, in the amended pCSR, information regarding the number of subjects in each treatment group with each category of protocol deviations was not provided. This information is important to assess whether the incidence of protocol deviations was comparable between treatment groups.

4. Please put forward possible explanations for the subgroup analysis results which showed no statistically significant difference between treatment groups across all efficacy endpoints in the subgroup of subjects with baseline LBBB.

Rationale for question above:

As noted above, subgroup analyses of the morbidity endpoints showed that there was no obvious pattern indicating that eplerenone was definitively less effective in certain subgroups across the endpoints, except for the subgroups of subjects with prior beta-blocker plus ACE-I plus ARB use, subjects without prior beta-blocker use, subjects without prior ACE-I or ARB use, subjects with baseline LBBB, and subjects with prior hospitalisation of ≥ 180 days. It is noted that the sample size in these subgroups were all small, except for that of subjects with baseline LBBB, which had 888 subjects. In the subgroup of subjects with baseline LBBB, analyses of all endpoints yielded results that showed no statistically significant difference between treatment groups. The sponsor did not provide any explanation regarding the lack of efficacy in this particular subgroup of subjects with baseline LBBB.

9.2. Safety

1. Please provide a tabulation or summary of the incidences of treatment-related deaths as well as of the incidence of each cause of death, for the amended pCSR, sCSR and OLE report.

Rationale for question above:

As commented above, although the sponsor has provided a list of the deaths for all 3 sets of CSRs, it was not clearly summarised or indicated as to which deaths were considered related to study treatment, and the incidence of each cause of death was not summarised. As a result the incidence of treatment-related deaths and of each cause of death could not be compared between the eplerenone and placebo groups.

2. Please provide a tabulation or summary of the incidences of treatment-related SAEs for the amended pCSR and the sCSR.

Rationale for question above:

As noted previously in this evaluation, in both the amended pCSR and the sCSR, a list of the most frequently reported treatment-related SAEs was not clearly tabulated or summarised.

3. Please provide additional safety analyses for the subgroup of patients with baseline LBBB present.

Rationale for question above:

As commented previously, subgroup efficacy analyses showed that for the subgroup of subjects with baseline LBBB, analyses of all efficacy endpoints yielded results that showed no statistically significant difference between treatment groups. It was recommended that a safety analysis be done in this subgroup in order to evaluate the risk-benefit profile for the use of eplerenone in this subgroup.

4. Please provide analysis of the responder rates in terms of reductions in SBP and DBP in the overall study population as well as in the age-stratified subgroups (≥ 75 years and < 75 years).

As noted previously, decreases in systolic and diastolic blood pressure were statistically significantly more in the eplerenone group compared to the placebo group in the overall study population. Although this is a known adverse effect of eplerenone, it was recommended that further analysis comparing the responder rates in terms of reductions in SBP and DBP be done and presented to allow better evaluation of the hypotensive effect of eplerenone. In particular, analyses in the subgroup of patients aged ≥ 75 years showed that the mean decrease from baseline in SBP and DBP at final follow-up assessment in the eplerenone group in this subgroup was greater compared to the overall study population and to the subgroup of patients aged < 75 years. It was recommended that further analysis comparing the responder rates in terms of reductions in SBP and DBP in these age-stratified subgroups (≥ 75 years and < 75 years) be done and presented in order to fully evaluate if eplerenone has a greater risk of hypotension in the elderly patient population. This would allow evaluation on the need for a precaution to be added in the proposed PI with regards to risk of hypotension or necessity for closer BP monitoring in the elderly patients.

10. Second round evaluation of clinical data submitted in response to questions

Overall, the sponsor has adequately addressed all the questions posed in the first round of evaluation. The evaluator is in disagreement with the sponsor's conclusion in relation to efficacy Question 4, but it does not impact the recommendation for this submission. Evaluation of the additional clinical data submitted by the sponsor in response to safety Question 4 raised some concern on the effect of eplerenone on the blood pressure of elderly patients, triggering a recommendation to amend the proposed PI (this will be described under the subheading "Safety Question 4"). The responses by the sponsor to the other questions did not raise new efficacy or safety concerns.

In this section on the evaluation of the sponsor's responses to the questions posed in the first round of evaluation, each question will be re-stated for ease of reference, followed by the evaluation.

Efficacy question 1

The response by the sponsor adequately clarified that the inclusion of subjects with eGFR of 30 to 49 mL/min/1.73 m² had been planned prospectively with the intention of evaluating the efficacy and safety in this group of patients. The Executive Steering Committee for the Emphasis-HF Study had made the decision to evaluate prospectively patients with moderate renal impairment at a lower dose of eplerenone, based on post-hoc analysis results from the EPHEBUS trial.

Efficacy question 2

The response by the sponsor has satisfactorily addressed the question. The dose had been chosen empirically with the aim of being an efficacious dose while avoiding the risk of hyperkalemia, which was a known adverse effect of eplerenone. A post-hoc analysis of the EPHEBUS trial evaluating the effect of eplerenone in patients receiving either 25 mg daily or 25 mg every other day suggested that eplerenone at a dose of 25 mg every other day, could be efficacious²².

Efficacy question 3

The sponsor provided data which showed that the number of subjects with each category of protocol deviations was comparable between treatment groups.

Efficacy question 4

The sponsor has stated that the total number of subjects with left bundle branch block (LBBB) at baseline was 688 and not 888, as described in the first round evaluation report. On review, the evaluator acknowledged that the figure should be 688. However, the figure of 888 had been drawn from Figure 6 on page 70 of the amended pCSR submitted by the sponsor. It is recommended that the sponsor make the relevant amendment to Figure 6 in the amended pCSR.

The sponsor had reproduced the subgroup efficacy tables previously submitted in the amended pCSR and which had been previously evaluated, and had stated that *“For the secondary endpoint of all-cause mortality or heart failure hospitalization, 84 (24.8%) in the eplerenone group (n=339), and 111 (31.8%) in the placebo group (n=349) met this endpoint, resulting in a significant relative risk reduction of 25.4% (p<0.0344, CI 0.562, 0.991). Similarly, for the secondary endpoint of all-cause mortality, 46 (13.6%) in the eplerenone group (n=339) and 68 (19.5%) in the placebo group (n=349) met this endpoint, resulting in a significant relative risk reduction of 33.3% (p<0.0344; CI 0.459, 0.971)”*.

The evaluator would like to bring to attention that, for the secondary endpoint of all-cause mortality or heart failure hospitalisation, the p value was 0.0430 and not <0.0344. It should also be noted that in accordance with the description in the study statistical methods, results were considered statistically significant if a p-value <0.049 was obtained for the primary endpoint, and p-value <0.01 for the secondary endpoints. Hence, the results for the 2 secondary endpoints quoted by the sponsor were not considered statistically significant.

The results of the subgroup analyses on the primary and secondary efficacy endpoints in the amended pCSR had been summarised in the first round evaluation report, and the relevant part concerning the subgroup of baseline LBBB present versus not present is reproduced below in Table 4 (with the sample size amended) for ease of reference. Results showed that in the subgroup of subjects with LBBB at baseline, analyses of the primary and main secondary

²² Banas et al. Favorable outcomes with 25 mg of eplerenone in patients with post-AMI heart failure: Results from the EPHEBUS Trial. J Card Fail 2005;1(Suppl):S156, Abstract 249

endpoints had all yielded results which were not statistically significant, compared to those in the subgroup of subjects without LBBB at baseline, where results were mostly statistically significant in favour of eplerenone, and this had prompted the question to the sponsor in the first evaluation report.

Table 4. Primary and main secondary endpoints in the subgroups of subjects with and without LBBB at baseline, study A6141079 (amended pCSR)

Endpoints	Baseline LBBB present			
	Yes N=688		No N=2048	
	Hazard Ratio	P value	Hazard Ratio	P value
HF hospitalisation or CV death (Primary endpoint)	0.751	0.0541	<u>0.623</u>	<u>< 0.0001</u>
All-cause mortality or HF hospitalisation	0.746	0.0430	<u>0.649</u>	<u>< 0.0001</u>
All cause mortality	0.667	0.0344	0.824	0.1141
CV mortality	0.671	0.0521	0.811	0.1118
All-cause hospitalisation	0.891	0.3678	<u>0.747</u>	<u>0.0002</u>
HF hospitalisation	0.869	0.4255	<u>0.523</u>	<u>< 0.0001</u>
All-cause death or all-cause hospitalisation	0.794	0.0520	<u>0.753</u>	<u>0.0001</u>
HF death or HF hospitalisation	0.869	0.4255	<u>0.527</u>	<u>< 0.0001</u>
CV hospitalisation	0.713	0.0177	<u>0.717</u>	<u>0.0002</u>

Values that are underlined and in blue are statistically significant.

It is acknowledged that the study was not powered for the subgroup analyses and that the sample size for the subgroup of subjects with LBBB at baseline was relatively small compared to the subgroup of subjects without LBBB at baseline. The question had been raised as a matter of academic curiosity, to explore if the sponsor had any possible explanations for this observation. The sponsor's response to "Safety Question 3" regarding the safety results in the subgroup of subjects with LBBB at baseline (described later), showed that there were no major safety concerns in this subgroup of subjects. Hence, although the evaluator disagrees with the sponsor's conclusion that "*subjects with left bundle branch block (LBBB) at baseline experienced a significant benefit from treatment with eplerenone*" this does not affect the recommendation for this submission.

Safety question 1

The additional data provided by the sponsor in response to this question did not raise any significant safety concerns. The sponsor had stated in their response that as the sCSR contained the full double-blind dataset, their response will be directed towards the sCSR and the OLE only.

This is deemed by the evaluator to be appropriate. The sponsor did not provide a direct summary of the incidences of treatment-related deaths and of the incidence of each cause of death, but had provided a summary of the incidences of all-cause SAEs and treatment-related SAEs occurring within 14 days of a death, and of deaths due to unknown cause as surrogate information. The sponsor did not state clearly in their response regarding why direct data was not provided. It is assumed by the evaluator that this was not recorded during the study and hence unavailable. In the absence of direct data, the surrogate information provided is deemed acceptable.

In the full-double-blind dataset in the sCSR, the number of all-cause SAEs reported within 14 days prior to a death was comparable between treatment groups (346 and 442 in the eplerenone and placebo group, respectively). The most commonly reported SAE in the eplerenone group was cardiac failure, and the incidence was comparable between treatment groups (40.5% [83/205] and 35.6% [90/253] in the eplerenone and placebo group, respectively). The number of treatment-related SAEs reported within 14 days prior to a death was also comparable between treatment groups (7 and 6 in the eplerenone and placebo group, respectively). The most commonly reported SAE in the eplerenone group was hyperkalaemia (1.0% [2/205] versus 0.0% [0/253] in the placebo group). Of the subjects who died during the double blind phase of the study, 2 deaths in the placebo group and 1 death in the eplerenone group were reported with cause unknown, and therefore attributed to the study medication by the sponsor.

In the OLE dataset, there were 78 all-cause SAEs reported within 14 days prior to a death. The most commonly reported SAE was cardiac failure, reported in 11 subjects (19.6%; 11/56). Three treatment-related SAEs in 3 subjects were reported within 14 days prior to a death in the OLE dataset. Two of these were in the preferred term of “deaths”, and 1 in the preferred term of “malignant neoplasm of ampulla of Vater”. Of the subjects who died during the OLE phase of the study, 2 deaths were reported with “cause unknown” and therefore attributed to the eplerenone treatment, and one death was reported with cause “Other,” and therefore was not attributed to the study treatment.

Safety question 2

The additional data provided by the sponsor in response to this question did not raise any significant safety concerns.

In the pCSR 37 (2.7%) subjects in the eplerenone group had 50 treatment-related SAEs compared to 30 (2.2%) subjects in the placebo group who reported 38 treatment-related SAEs. The most-frequently reported treatment-related SAEs in the eplerenone group were hyperkalaemia (0.9% [12/1360] versus 0.2% [3/1369] in the placebo group), cardiac failure (0.4% [5/1360] versus 0.2% [3/1369]), and renal impairment (0.4% [5/1360] versus 0.4% [5/1369]).

For the complete double-blind phase in the sCSR, 39 (2.9%) subjects in the eplerenone group had 52 treatment-related SAEs compared to 29 (2.1%) subjects in the placebo group who reported 36 treatment-related SAEs. The most-frequently reported treatment-related SAEs in the eplerenone group were hyperkalaemia (0.9% [12/1364] versus 0.2% [3/1372] in the placebo group), renal impairment (0.4% [5/1364] versus 0.4% [5/1372]), and cardiac failure (0.3% [4/1364] versus 0.2% [3/1372]).

Safety question 3

The additional data provided by the sponsor in response to this question did not raise any significant safety concerns for this subgroup of subjects. The safety results in this subgroup of

subjects were generally comparable with those for the overall study population (see Table 5 below).

In the complete double-blind phase, there were 339 subjects in the eplerenone group and 349 in the placebo group with LBBB at baseline. In this subgroup, 257 subjects (75.8%) in the eplerenone group and 262 subjects (75.1%) in the placebo group experienced 930 and 932 AEs of any cause, respectively. The most commonly reported all-causality AEs in the eplerenone group were cardiac failure (eplerenone versus placebo: 22.1% versus 24.6%), hyperkalaemia (9.1% versus 3.7%), and renal impairment (5.0% versus 2.9%). In this subgroup of subjects with LBBB at baseline, 79 subjects (23.3%) in the eplerenone group and 58 subjects (16.6%) in the placebo group experienced 116 and 91 treatment-related AEs, respectively. The most commonly reported treatment-related AEs in the eplerenone group were hyperkalaemia (eplerenone versus placebo: 8.3% versus 2.6%), hypotension (1.8% versus 0.0%), and renal impairment (1.5% versus 1.4%).

With regards to all-cause SAEs, 147 subjects (43.4%) in the eplerenone group and 173 subjects (49.6%) in the placebo group experienced 326 and 392 all-causality SAEs, respectively. The most commonly reported SAEs in the eplerenone group were cardiac failure (eplerenone versus placebo: 20.1% versus 20.9%), pneumonia (2.7% versus 1.7%), and renal impairment (2.7% versus 1.7%). With regards to treatment-related SAEs 11 subjects (3.2%) in the eplerenone group and 9 subjects (2.6%) in the placebo group experienced 14 and 12 treatment-related SAEs, respectively. The most commonly reported SAEs in the eplerenone group were hyperkalaemia (eplerenone versus placebo: 1.8% versus 0.0%), cardiac failure (0.9% versus 0.3%), and renal impairment (0.6% versus 0.9%).

Table 5. Summary of safety results in the complete double-blind phase dataset in the overall population and in the subgroup of subjects with LBBB at baseline.

	Complete double-blind phase dataset (sCSR), subgroup of subjects with LBBB at baseline		Complete double-blind phase dataset (sCSR), overall population	
	Eplerenone N=339	Placebo N=349	Eplerenone N=1364	Placebo N=1372
Incidence of all-causality AEs	75.8%	75.1%	76.8%	78.1%
Incidence of treatment-related AEs	23.3%	16.6%	21.3%	17.1%
Incidence of all-causality SAEs	43.4%	49.6%	43.0%	50.0%
Incidence of treatment-related SAEs	3.2%	2.6%	2.9%	2.1%
Most commonly reported all-causality AEs in the eplerenone group	- cardiac failure (22.1% versus 24.6% in the placebo group) - hyperkalaemia (9.1% versus 3.7% in the placebo group) - renal impairment (5.0% versus		- cardiac failure (20.5% versus 23.8% in the placebo group) - hyperkalaemia (8.7% versus 4.0% in the placebo group) - dyspnoea (5.0% versus 5.5% in	

	Complete double-blind phase dataset(sCSR), subgroup of subjects with LBBB at baseline		Complete double-blind phase dataset (sCSR), overall population	
	Eplerenone N=339	Placebo N=349	Eplerenone N=1364	Placebo N=1372
	2.9% in the placebo group).		the placebo group) - renal impairment (5.0% versus 3.2% in the placebo group)	
Most commonly reported treatment-related AEs in the eplerenone group	- hyperkalaemia (8.3% versus 2.6% in the placebo group)		- hyperkalemia (7.0% versus 2.9% in the placebo group)	
Most commonly reported all-causality SAEs in the eplerenone group	- cardiac failure (20.1% versus 20.9% in the placebo group)		- cardiac failure (16.0% versus 19.7% in the placebo group)	
Most commonly reported treatment-related SAEs in the eplerenone group	- hyperkalaemia (1.8% versus 0.0% in the placebo group) - cardiac failure (0.9% versus 0.3% in the placebo group) - renal impairment (0.6% versus 0.9% in the placebo group)		- hyperkalaemia (0.9% versus 0.2% in the placebo group) - renal impairment (0.4% versus 0.4% in the placebo group) - cardiac failure (0.3% versus 0.2% in the placebo group).	

Safety question 4

The additional data provided by the sponsor suggested that eplerenone may be associated with a greater drop in systolic BP in patients aged ≥ 75 years.

The sponsor did additional post-hoc analyses in the complete double-blind phase database on the maximum reduction from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured at any time post randomisation, and presented results of incidences in the categories of no reduction, reductions of 1-5 mmHg, reductions of 6–10 mmHg, reductions of 11– 20 mmHg, greater than 20 mmHg reduction, and missing values. These post-hoc analyses results provided by the sponsor showed that among subjects aged < 75 years, the proportion of subjects with each category of reductions in SBP and DBP was generally comparable between the eplerenone and the placebo group (see Table 6). Among subjects aged ≥ 75 years, the proportion of subjects in each category of reductions in SBP and DBP was also generally comparable between the eplerenone and the placebo group, except for the category of reductions > 20 mmHg, for both SBP and DBP (see Table 7). In the category of reductions in SBP > 20 mmHg, the incidence in the eplerenone group was 37.9% compared with 24.4% in the placebo group, while in the category of reductions in DBP > 20 mmHg, the incidence in the eplerenone group was 14.2% compared with 8.8% in the placebo group. Comparing the results between age groups (< 75 years versus ≥ 75 years), the proportion of subjects in each category of reductions in SBP and DBP was generally comparable between the 2 age groups in both the eplerenone and the placebo treatment groups, except for the category of reductions > 20 mmHg

for SBP, where the incidence in the eplerenone group was 37.9% for subjects aged ≥ 75 years, compared with 28.3% for subjects aged < 75 years. For the placebo group, the proportion of subjects in this category of reductions > 20 mmHg for SBP was comparable between the 2 age groups (24.4% for subjects aged ≥ 75 years, and 23.9% for subjects aged < 75 years).

Table 6. Maximum systolic/diastolic blood pressure reduction from baseline - patients age < 75 (based on complete DB phase database), study A6141079

Maximum Reduction (mmHg)	Systolic BP		Diastolic BP	
	Inspira (N=1037)	Placebo (N=1048)	Inspira (N=1037)	Placebo (N=1048)
No reduction	181 (17.5)	193 (18.4)	253 (24.4)	267 (25.5)
1 - 5	91 (8.8)	121 (11.5)	127 (12.2)	144 (13.7)
$>5 - 10$	181 (17.5)	196 (18.7)	255 (24.6)	266 (25.4)
$>10 - 20$	275 (26.5)	270 (25.8)	263 (25.4)	248 (23.7)
>20	293 (28.3)	250 (23.9)	123 (11.9)	105 (10.0)
Missing	16 (1.5)	18 (1.7)	16 (1.5)	18 (1.7)

Table 7. Maximum systolic/diastolic blood pressure reduction from baseline - patients age ≥ 75 (based on complete DB phase database), study A6141079

Maximum Reduction (mmHg)	Systolic BP		Diastolic BP	
	Inspira (N=330)	Placebo (N=328)	Inspira (N=330)	Placebo (N=328)
No reduction	47 (14.2)	65 (19.8)	56 (17.0)	66 (20.1)
1 - 5	22 (6.7)	21 (6.4)	51 (15.5)	42 (12.8)
$>5 - 10$	46 (13.9)	57 (17.4)	71 (21.5)	95 (29.0)
$>10 - 20$	85 (25.8)	98 (29.9)	100 (30.3)	89 (27.1)
>20	125 (37.9)	80 (24.4)	47 (14.2)	29 (8.8)
Missing	5 (1.5)	7 (2.1)	5 (1.5)	7 (2.1)

The sponsor also did a categorical assessment of the incidence of subjects with measured blood pressures at any time post randomisation of less than 90 mmHg systolic or 50 mmHg diastolic, regardless of symptom presentation. The results showed that the incidences were comparable between the age groups of < 75 years and ≥ 75 years (see Table 8 below).

Table 8. Incidence of patients exhibiting SBP < 90 or DBP < 50 post-baseline (based on complete DB phase database), study A6141079

Age Group	Inspira (N=1367)	Placebo (N=1376)
All patients	120 (8.8)	72 (5.2)

Age Group	Inspira (N=1037)	Placebo (N=1048)
Age < 75	92 (8.9)	54 (5.2)

Age Group	Inspira (N=330)	Placebo (N=328)
Age ≥ 75	28 (8.5)	18 (5.5)

The sponsor acknowledged in their response that there “*may be an age related component. As is often the case, in the absence of definitive data, there may be a greater sensitivity to treatment in older individuals, with appropriate clinical monitoring and oversight potentially prudent based on individual clinical presentation*”. However, the sponsor stated that the term “hypotension” has been included in the proposed PI as “Common” in the Adverse Effects section, and that they would therefore not be proposing to add a “Precaution”

related to these post hoc observations “*given the current proposed product information already informs of relative incidence of the AE from the study, which is more clinically relevant than the post hoc numerical reductions discussed here*”.

The evaluator noted that hypotension has been included as a common adverse event in the proposed PI. However, although these post-hoc observations were not definitive, they suggested that eplerenone may be associated with a greater drop in systolic BP in patients aged ≥ 75 years. Clinicians prescribing eplerenone will be guided by the PI in deciding the frequency of monitoring of BP. Given that these observations suggested that there may be greater sensitivity to treatment in older patients who may therefore need closer BP monitoring, it is recommended that a statement stating that “*post-hoc analyses in the EMPHASIS-HF study suggested that there may be a greater sensitivity to treatment in older individuals and thus potentially greater reductions in blood pressure with the use of eplerenone compared to younger individuals*” be added as a precaution to the heading of “*Use in elderly*” in the proposed PI.

11. Second round benefit-risk assessment

11.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of eplerenone in the proposed usage are unchanged from those identified in the First Round Evaluation.

11.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of eplerenone in the proposed usage are unchanged from those identified in the First Round Evaluation.

11.3. Second round assessment of benefit-risk balance

The benefit-risk balance of eplerenone, given the proposed usage, was considered to be favourable.

12. Second round recommendation regarding authorisation

It is recommended that the application for extension of indication of eplerenone for treatment of adult patients with NYHA class II chronic heart failure, as an addition to standard optimal therapy, be approved.

This is subject to a satisfactory response to the recommended changes in the PI raised by the evaluator.

13. References

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